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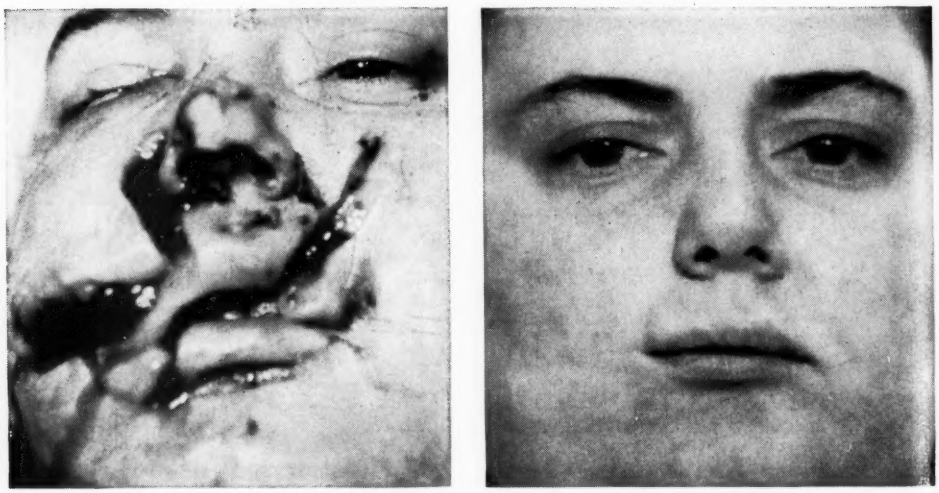
*Straith, C. L., and Straith, R. E.: Detroit, Michigan. Postgrad. Med. *14*:165, Sept., 1953.



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THYROID ACTIVITY DURING OPERATION

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THE MANY FACETS of the endocrinologic response to trauma have not been completely delineated at present despite extensive research. Diverse patterns of thyroid-adrenocortical response to operation have been described and increased activity of the thyroid gland has been demonstrated by the increased glandular uptake of radioiodine following operation by Goldenberg and associates (3, 5). The present study was designed to evaluate thyroid activity during operation by determining protein-bound radioiodine (PBI^{131}) as reflecting the level of circulating thyroid hormone and as a prompt indicator of the time sequence changes in thyroid activity during trauma.

MATERIALS AND METHODS

Sixteen patients of varying ages undergoing 17 operative procedures were studied (Table I). Each patient was given a tracer amount of I^{131} 48 to 72 hours prior to operation thus permitting equilibration and maximal protein-binding of the radioactive material before operation. The 24 hour uptake of the I^{131} by the thyroid gland was calculated as an evaluation of the preoperative level of thyroid activity.

On the day of operation blood samples for PBI^{131} determinations were drawn prior to administration of the preanesthetic medication, after premedication, during the induction of anesthesia and during the operative procedure at intervals varying between 20 and 45 minutes. All but 2 patients were given general, endotracheal anesthesia; one received spinal and the other local field block. Further blood samples were drawn at the time of the tracheal extubation and when the patient was fully awake, usually from 1 to 2 hours after completion of the operation. Several patients were followed at greater lengths by serial postoperative PBI^{131} determinations.

Protein-bound iodine was extracted from 2 milliliters of serum by a modification of the method of Barker and associates and the radioactivity of each specimen was counted in a scintillation well detector. Counting times up to 20 minutes per sample were used in order to obtain statistically valid counts. Crude serum was counted in a similar manner and

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TABLE I

Patient	*Age*	*Operation*	*Per cent 24 hr. I^{131} uptake*	*Chronic illness or recent acute stress*	*Preop. conversion ratio*	*Maximum conversion ratio*
A	50	Inguinal hernia repair	34	No	49	66
B	68	Sigmoid resection	35	No	31	55
C	48	Subtotal gastrectomy	30	No	21	69
D	39	Hemorrhoidectomy	49	No	53	82
E	72	Subtotal gastrectomy	42	No	3	33
F	40	Simple mastectomy	41	No	33	52
G	35	Pneumonectomy	40	No	45	81
H	65	Transverse colectomy	34	Cecostomy for bowel obstruction; colectomy 12 days later	28	38
I	46	Hemorrhoidectomy	69	Chronic preop. blood loss	74	81
J	71	Sigmoid resection	47	Inguinal hernia repair; carcinomatous peritoneal implant. Colon resection 19 days later	55	59
K	62	Subtotal gastrectomy	34	Marked weight loss; symptomatic gastric ulcer, chronic alcoholism	65	71
L	78	Right colectomy	32	Acute appendicitis; carcinoma appendix. Colectomy 23 days later	4	9
M	62	Inguinal hernia repair	37	Chronic nephritis; poor nutrition	64	64
N	67	Sigmoid resection	26	Chronic blood loss; marked weight loss	61	67
O	38	Pneumonectomy	31	Far advanced pulmonary tuberculosis with cavitation	48	49
P	51	1st op.: ileosigmoidostomy	49	Multiple colon polypi	47	75
		2nd op.: subtotal colectomy	52		59	65

the conversion ratio computed according to the method of Clark and his co-workers. In the present study this procedure was considered to represent the simplest and most accurate method of expressing the circulating thyroid hormone as:

$$\text{Conversion ratio} = \frac{\text{net counts of PBI}^{131} \text{ in 2 ml. serum}}{\text{net counts in 2 ml. serum}} \times 100.$$

A patient was considered to have increased thyroid hormone levels during operation if the conversion ratio increased more than 10 units (arbitrarily chosen) over the earliest preoperative determination.

Hematocrit measurements and total serum protein levels were determined on each blood sample in an attempt to exclude blood dilution or changes in protein composition as possible reasons for alterations in PBI^{131} levels noted. Mechanical difficulty with venipunctures limited the number of samples taken in some of the patients.

RESULTS

The patients in this study were found to fall into two groups: those who showed increased thyroid activity by increased conversion ratios during operation, and those who did not. In general, the patients who did not respond with thyroid activation during operation were those who had chronic illness or recent acute trauma prior to the operation studied (Fig. 1). Patient I had chronic blood loss from her extensive hemorrhoids and transfusions were necessary preoperatively while patient K had a long-standing symptomatic gastric ulcer with marked weight loss in addition to chronic alcoholism before operation. Chronic nephritis and poor nutrition were present in patient M whose very large inguinal hernia was repaired under local field block. An extreme degree of weight loss and chronic rectal blood loss were present prior to sigmoid resection for adenocarcinoma in patient N. Patient O had far-advanced pulmonary tuberculosis for a period of many years before pneumonectomy became necessary because of residual cavitation.

Several patients who did not have thyroid activation had operations performed a short time before the definitive surgical procedure which was studied here. Patient H had signs of large bowel obstruction for which an emer-

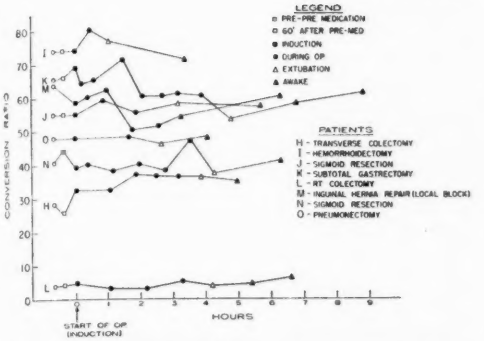

FIG. 1. Thyroid nonreactors with chronic illness or recent acute trauma prior to operation studied here.

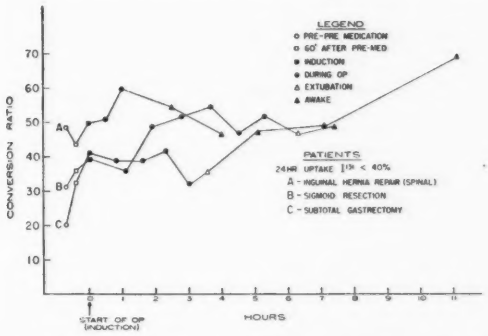

FIG. 2. Thyroid reactors with 24 hour I^{131} uptake of less than 40 per cent.

gency cecostomy was performed followed 12 days later by resection of a carcinoma of the transverse colon. Patient J underwent repair of an inguinal hernia at which time a carcinomatous peritoneal implant was found necessitating large bowel resection for asymptomatic carcinoma 19 days later. Adenocarcinoma of the appendix was discovered in patient L after appendectomy for acute appendicitis which was treated 23 days later by right colectomy.

When chronic illness and prior acute stress were absent as in Patients A through G an increase in thyroid activity occurred during operation (Figs. 2 and 3). Patient A had an elective repair of an inguinal hernia while patient B had an essentially asymptomatic sigmoid colon carcinoma resected. Gastric ulceration (possibly carcinoma by roentgenogram) was discovered in patients C and E after a few symptoms had been noted and subtotal gastrectomy was performed in each without carcinoma being found. Moderately severe hemorrhoids prompted patient D to have an elective hemorrhoidectomy while patient F had a prophylactic simple mastectomy performed for extensive chronic cystic mastitis. Patient G had carcinoma of the breast treated by radical extirpation after which she was asymptomatic for about 18 months prior to pneumonectomy for a solitary pulmonary metastasis which treatment enabled her to live quite comfortably for many months.

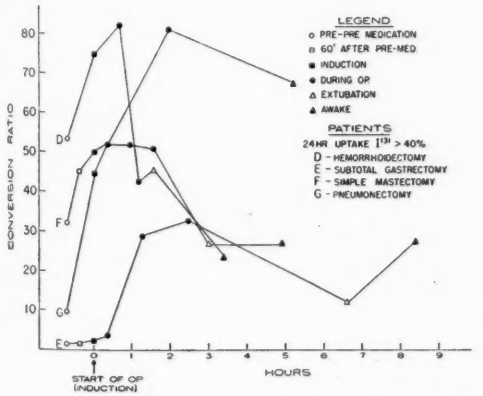

FIG. 3. Thyroid reactors with 24 hour I^{131} uptake of more than 40 per cent.

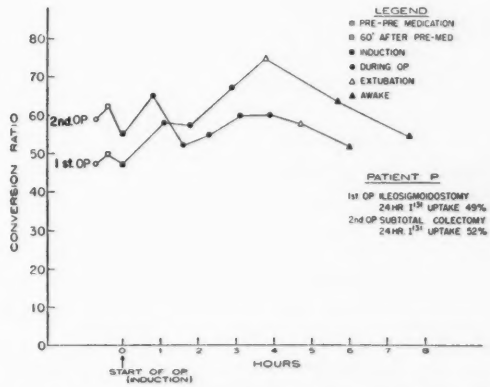

FIG. 4. Patient P displayed thyroid response after the first operation but not after the second 48 days later.

Patient P (Fig. 4) was studied through two major operations. Multiple colonic polypi were present and the first operation studied here, ileosigmoidostomy, resulted in increased thyroid activity while the second operation 48 days later, subtotal colectomy, did not.

It should be noted here that in no patient did the hematocrit vary more than 3 per cent, and in only 1 patient did protein levels change as much as 1.0 gram per cent in any two blood samples analyzed.

DISCUSSION

An increase in the conversion ratios following the onset of surgical trauma in this study corroborates the previous observations suggesting increased thyroid activity as a consequence of operation. The increase in thyroid activity apparently can be interpreted as part of the normal response to operation. When such abnormal long-standing disease states as chronic hemorrhage, debilitating illness, poor nutrition, and weight loss are present, the thyroid response is decreased or absent. The effects of acute stress in altering the metabolic-endocrine responses to subsequent episodes of trauma are also important. Initial effects brought about by a traumatic episode do not disappear quickly as noted by Moore and Ball and until complete restitution to normal of all the participating endocrine changes has been made, there will not be thyroid activation when further stress occurs. This concept is emphasized by the patients reported here who had surgical procedures shortly before undergoing a second operation (which was studied here with PBI^{131} levels) and who did not show activation of the thyroid gland after the second operation. Patient P (Fig. 4) is also a good example of this phenomenon responding with thyroid activation after the first operation was performed but displaying no thyroid response subsequent to the second surgical procedure.

The level of thyroid activity before operation appeared to have some influence on the stress response. Those patients who had glandular uptake of radioiodine of 40 per cent or more after 24 hours (high euthyroid) (patients D, E, F, G, P; Figs. 3 and 4) had a much greater thyroid activation in general than those whose uptakes were less than 40 per cent. Age apparently had little effect on thyroid activation as did also the degree of trauma. Young and old, minor and major degrees of surgical trauma are all included among those patients in this study who had thyroid activation as well as those who did not.

After an increase in the conversion ratio at some time early in the operation a fall to preoperative or lower than preoperative levels followed in most patients. This suggests a decrease in production of thyroid hormone or increased utilization of hormone at the cellular level. Antagonism of adrenocortical hormone for thyroid glandular activity as demonstrated by Goldenberg and associates (4) may also play a part here and many of these patients who showed a subsequent decrease in the conversion ratio may have had adrenocortical responses of some marked degree.

Patients B, C, E, and G (Figs. 2, 3) never returned to preoperative conversion ratio levels for the period of observation after operation and may represent one of the patterns of response which were described earlier, thyroid activation without adrenocortical activation.

The stability of the hematocrit and total protein determinations suggests that neither blood dilution nor alterations in protein composition present for iodine-binding altered the results found here. The elevated conversion ratio levels observed would certainly have been more elevated had dilution from intravenous fluids during operation indeed played a part. By the same token, possibly those patients who showed no increase in conversion ratio would have shown some increase.

CONCLUSIONS

An increase in circulating thyroid hormone as measured by the conversion ratio

(PBI^{131}) has been demonstrated to be present in a group of patients during operative trauma. Patients who had chronic illness or recent acute stress prior to the study did not show increased conversion ratios during operation.

The present study as well as previous work suggests that thyroid activation may play a very important role in the entire endocrine-metabolic response to operative stress. In the absence of thyroid response, the entire chain of poststress events in the organism may be quite different from the standardized descriptions.

REFERENCES

1. Barker, S. B., Humphrey, M. J., and Soley, M. H. The clinical determination of protein-bound iodine. J. Clin. Invest., 1951, 30: 55–62.
2. Clark, D. E., Moe, R. H., and Adams, E. E. The rate of conversion of administered inorganic radioactive iodine into protein-bound iodine of plasma in the evaluation of thyroid function. Surgery, 1949, 26: 331–340.
3. Goldenberg, I. S., Lutwak, L., Rosenbaum, P. J., and Hayes, M. A. Thyroid-adrenocortical interrelations following operation. Surg. Gyn. Obst., 1954, 98: 513–522.
4. Idem. Thyroid-adrenocortical metabolic interrelations. J. Clin. Endocr., 1955, 15: 227–237.
5. Goldenberg, I. S., Rosenbaum, P. J., and Hayes, M. A. Patterns of thyroid-adrenocortical response after operation. Ann. Surg., 1955, 142: 786–797.
6. Moore, F. D., and Ball, M. R. The Metabolic Response to Surgery. Springfield, Ill.: Charles C Thomas, 1952.

STUDIES ON HYPOTHERMIA IN MONKEYS

II. The Effect of Hypothermia on the General Physiology and Cerebral Metabolism of Monkeys in the Hypothermic State

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THE PHYSIOLOGIC BASIS for the clinical application of hypothermia in surgery has been derived from animal experimentation and slowly increasing experience in patients. The metabolic studies which have been reported were often done during active cooling and observations made prior to physiologic stabilization. Therefore, it seemed that a detailed study of the general response of monkeys to hypothermia, and more particularly changes in cerebral metabolism during a period of physiologic stabilization, would be a valuable guide to the proper management of surgical patients.

MATERIALS AND METHODS

Monkeys (Macaca mulatta) of either sex, 12 to 18 months of age, and 2 to 5 kilograms in weight were used for this study. Thirteen monkeys were used in the study of cerebral blood flow and cerebral oxygen consumption, and 7 were used to obtain data on the utilization of sugar.

The animals were anesthetized with intravenous pentobarbital sodium in amounts ranging from 12 to 25 milligrams per kilogram. The depth of anesthesia was controlled by electroencephalogram (EEG) so that the final depth of sleep recorded on the EEG would be the same regardless of the body temperature.

Hypothermia was induced in all monkeys by immersion in an ice water bath at 3 degrees C. A separate animal was used for each temperature studied; and after the animals had been cooled to the desired temperature, a stabilization period of about an hour was allowed to elapse before cerebral blood flow and cerebral oxygen consumption studies were done. A previous publication describes the methods of rewarming, maintenance of respiration, temperature recording, electrocardiography, and electroencephalography (4).

Cerebral blood flow determinations were made by the Kety-Schmidt nitrous oxide method (2, 3). This method had to be slightly modified by lengthening the sampling period to 15 minutes so that equilibration of the nitrous oxide could take place between arterial blood and brain tissue. Blood samples were taken through polyethylene tubes placed in the jugular bulb and a femoral artery. It has been shown by Kety and Schmidt that jugular bulb and sagittal sinus blood give the same blood flow with this method in monkeys (2). Blood arteriovenous oxygen and carbon dioxide differences were done in conjunction with the blood flow studies. Duplicate

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This study was sponsored in part by the Committee on Metabolism in Trauma, Commission on Liver Diseases, Armed Forces Epidemiological Board, and supported by the Surgeon General, Department of the Army, through a Contract (DA-49-007-MD-472) with Harvard University, and in part by grants B-157 and C-1608 from the National Institutes of Public Health. The generous assistance of the Samuel Cabot Fund is also gratefully acknowledged.

blood sugar determinations were carried out by microtechnique, using the method of Folin.

RESULTS

All of the animals cooled at a fairly uniform rate (Fig. 1). After the temperature had stabilized, it remained constant for several hours unless external heat was applied. During surgical procedures in which the animal was covered with drapes and under hot operating room lights the temperature rose slightly. All animals rewarmed rapidly in the 45 degree C. bath regardless of the procedure which had been carried out. None of the animals died as a result of cooling, nor were there any ill effects seen by follow-up EEG's and clinical observations.

The mean arterial blood pressure fell 10 to 30 millimeters of mercury as the temperature was reduced. The venous pressure (jugular bulb) change was inconsistent, but in general it did not vary significantly (Fig. 2). The ECG changes observed in this group of monkeys consisted of essentially four findings: (1) pulse rate was consistently slowed and appeared to be a direct function of the temperature decrease, (2) the Q-T interval progressively lengthened in all monkeys, (3) in some monkeys inversion of the T wave occurred, and (4) in some monkeys there was elevation of the S-T segment. No cardiac arrhythmias were seen. All of these physiologic alterations were reversed on rewarming. These results are in agreement with other investigations carried out in dogs.

The cerebral blood flow diminished with cooling, but there was a great variation between animals (Table I). The cerebral blood flow of monkeys at normal temperatures ranged from 77 to 26 cubic centimeters per 100 grams of brain tissue per minute with a mean of 40 cubic centimeters per 100 grams of brain tissue per minute; under hypothermic conditions the variation was almost equally great. The cerebral arteriovenous oxygen difference was directly related to the cerebral blood flow. It decreased

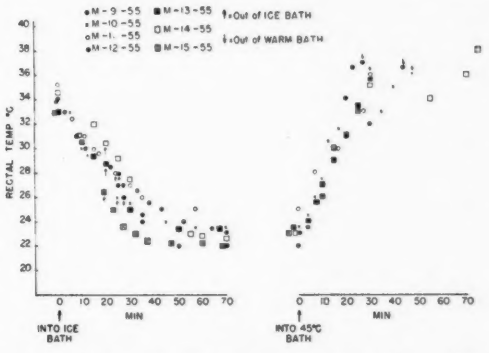

FIG. 1. Time for cooling and warming of monkeys under pentobarbital anesthesia.

with falling temperature, but if the cerebral blood flow was rapid, the arteriovenous oxygen difference was not as great as if the flow was very slow. For example, 1 monkey studied at 24.5 degrees C. had a cerebral blood flow of 40 cubic centimeters per 100 grams of brain tissue per minute and an arteriovenous oxygen difference of only 3.3 volumes per cent, while another monkey studied at 23 degrees C. had a blood flow of only 15 cubic centimeters per 100 grams of brain tissue per minute and had an arteriovenous oxygen difference of 6.4 volumes per cent. The arteriovenous carbon dioxide differences generally paralleled the oxygen differences.

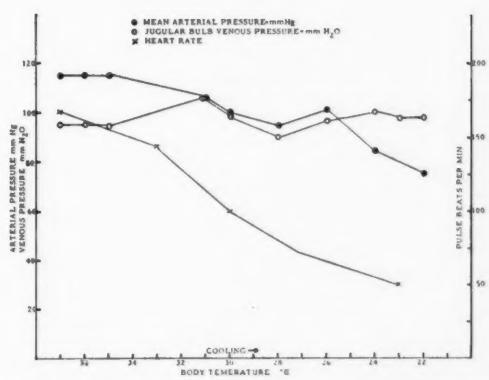

FIG. 2. Changes in heart rate, mean arterial blood pressure, and jugular bulb venous pressure seen during hypothermia. This curve represents the mean of data obtained from 20 monkeys.

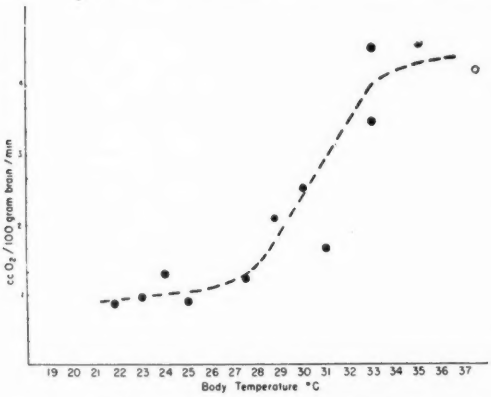

FIG. 3. The effect of hypothermia on cerebral oxygen consumption. Temperature is increasing from left to right.

Cerebral oxygen consumption calculated from these data shows very little change from the normal range of 2.5 to 4.7 cubic centimeters of oxygen per 100 grams of brain per minute until a temperature of about 31 degrees C. (88 degrees F.) was reached. At this temperature, a very sudden drop in the cerebral oxygen consumption occurred and this fall continued until 27 degrees C. (81 degrees F.) was reached. Below this temperature the cerebral oxygen consumption seemed to stabilize at a level of 0.8 to 1 cubic centimeter per 100 grams of brain per minute, or about 25 per cent of its normal value (Fig. 3). As cooling continued, the oxygen consumption fell very slowly.

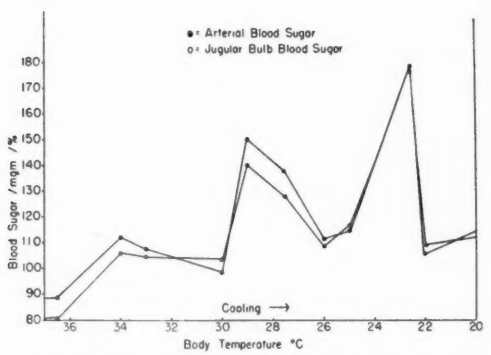

FIG. 4. Effect of hypothermia on blood sugar levels. This curve is a composite of data obtained in 20 monkeys.

The mean arterial and jugular bulb blood sugar levels increased in an irregular manner with cooling. At normal temperatures (36 degrees C.), the mean arterial blood sugar level was 87 milligrams per cent, at 34 degrees C., 112 milligrams per cent, at 30 degrees C., 98 milligrams per cent, at 29 degrees C., 150 milligrams per cent, at 26 degrees C., 105 milligrams per cent. The mean jugular bulb blood sugar levels in general paralleled those of the arterial blood, and in some instances were slightly higher (Fig. 4). The exact meaning of a jugular bulb blood sugar level higher than that of arterial blood is not clear; however, this observation suggests a change in glucose utilization at reduced body temperature. On rewarming, the blood sugar levels rapidly returned to normal.

DISCUSSION

It was shown in previous studies that one of the effects of cold was potentiation of pentobarbital anesthesia; and as body temperature decreased, smaller doses of anesthesia were required to achieve the same depth of sleep as measured by the EEG. In the present experiments, the level of anesthesia was measured by EEG and was kept as nearly constant as possible regardless of temperature so that the metabolic changes observed were a result of cooling and not the effect of anesthetic drugs. This conclusion is confirmed by the results which show a diminishing oxygen consumption with successively smaller doses of anesthesia, an effect opposite to that which would be expected to take place at normal body temperature.

The decrease in cerebral blood flow was accompanied by a calculated increase in the cerebral vascular resistance. The exact nature of this is not certain, but it was not related to either blood carbon dioxide or oxygen levels. It may have been the result of cerebral vascular spasm, or it is possible that it is an expression of increased blood viscosity and not related to the state of the cerebral blood vessels.

TABLE I.—DETAILED DATA ON THE CEREBRAL BLOOD FLOW AND CEREBRAL METABOLISM OF MONKEYS AT TEMPERATURES FROM 35 TO 22 DEGREES C.

Monkey No.	*Temperature, °C.*	*Mean arterial blood pressure, mm. Hg*	*Mean cerebral venous pressure, mm. H_2O*	*Cerebral blood flow, c.c./100 gm. brain/min.*	*A-V O_2 volume per cent*	*A-V CO_2 volume per cent*	*O_2 consumption, c.c. O_2 per 100 gm. brain per min.*	*R.Q.*	*Cerebral vascular resistance*
Mean of 22 monkeys....	37-35	115	95	40	8	8	4	1	
m-49-55....	35	120	90	77	6.05	7.42	4.6	1.2	1.4
m-52-55....	33	110	78	74	4.70	10.00	3.46	2.1	1.41
m-46-55....	32.5	75	105	57	7.90	8.90	4.5	1.1	1.2
m-45-55....	31	110	100	57	2.90	4.40	1.6	1.4	1.8
m- 9-55....	30	83	135	43	6.80	8.40	2.5	1.5	1.7
m-54-55....	29	117	85	29	7.10	9.30	2.1	1.3	1.8
m-40-55....	27.5	72	45	38	3.20	2.00	1.2	0.6	1.9
m- 7-55....	26.5	100	85	21	2.25	1.73	0.5	0.7	4.7
m-41-55....	25	50	65	27	3.30	3.00	0.9	0.9	1.65
m-55-55....	24.5	100	105	40	3.30	5.30	1.3	1.6	2.3
m-21-55....	23	70		15	6.4	6.1	0.96	0.95	
m-43-55....	22	54	100	17.5	5.0	4.4	0.88	0.88	2.6

It is important to note in considering the results of the oxygen consumption studies that these animals had been allowed to stabilize at the temperature studied, and that a separate animal was used for each point on the curve. There is probably some time lag for the temperature to become uniform throughout the body and for the biochemical processes to adjust to altered temperature, and this may account for the differences between these results and the linear relationship between body temperature and metabolism suggested by other studies done during the cooling period. However, in spite of the differences in the rate of change of metabolism, there is good agreement on the overall decrease in oxygen consumption at 26 degrees C. to about 25 to 30 per cent of its normothermic level.

The studies of sugar metabolism reported here which show a striking reduction at about 30 degrees C. are in agreement with the work of Wynn who found, in patients, that below 30 degrees C. glucose metabolism was markedly diminished. The reduction of both oxygen and sugar consumption by the brain at about the same temperature is to be expected for most of this oxygen is used in glucose metabolism. As the studies were done in different groups of animals, they tend to validate each other.

Additional evidence indicating that 30 degrees C. is a critical temperature in mammalian metabolism is furnished by the observations that cold narcosis often occurs at this temperature.

It is probable that anaerobic metabolic processes are also altered by cooling, for the tolerated period of afferent cerebral circulatory occlusion at 25 degrees C. is almost 5 times as long as at normal temperature (4), while oxygen consumption is only decreased one-third to one-fourth its normal value.

If oxygen metabolism and sugar utilization are taken as guides to the use of hypothermia, the maximum benefits are obtained between 28 and 29 degrees C., and there is little gained unless the patient is cooled to below 30 degrees C. If, however, the temperature is reduced to a level below 27 degrees C., there is a considerable risk of cardiac arrhythmia. In addition, likelihood of recovery after total occlusion of the circulation to the brain is reduced (4).

SUMMARY

1. The general physiologic effects of cooling on monkeys were studied. Cooling causes a diminution in the pulse rate and a slight decrease in mean blood pressure; it has little or no effect on the venous pressure, and there is a prolongation of the *Q-T* interval seen in the ECG.

2. At about 31 degrees there is a progressive decrease in the cerebral blood flow with

decreasing temperature. This does not exactly parallel the fall in blood pressure and is accompanied by a rise in cerebral vascular resistance.

3. The cerebral oxygen consumption drops sharply between 31 and 27 degrees C. from a normal range of 2.5 to 4.7 cubic centimeters per 100 grams of brain to between .8 to 1 cubic centimeter per 100 grams of brain per minute. There is little change below 27 degrees C.

4. The blood sugar levels increase almost 66 per cent over the normal resting levels. There is also a progressive drop in the arteriovenous cerebral blood sugar differences which suggests that below 30 degrees C. glucose metabolism is markedly reduced. This observation reflects the decrease in oxygen consumption.

5. These data and the work of others suggest that for surgical procedures the patients should be cooled to at least 30 degrees C. but not below 27 degrees C.

REFERENCES

1. Folin, O., and Svedberg, A. Micro methods for determination of non-protein nitrogen, urea, uric acid, and sugar in unlaked blood. J. Biol. Chem., 1930, 88: 85.
2. Kety, S. S., and Schmidt, C. F. Determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. Am. J. Physiol., 1945, 143: 53.
3. Idem. Nitrous oxide method for the quantitative determination of cerebral blood flow in man. J. Clin. Invest., 1948, 27: 476.
4. McMurrey, J. D., Bernhard, W. F., Taren, J. A., and Bering, E. A., Jr. Studies of hypothermia in monkey—I, the effect of hypothermia on the prolongation of the permissible time of total occlusion of the afferent circulation of the brain. Surg. Gyn. Obst., 1956, 102: 75.
5. Wynn, Victor. Electrolyte disturbances associated with failure to metabolise glucose during hypothermia. Lancet, Lond., 1954, 2: 575.

POSTOPERATIVE ACUTE PANCREATITIS

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ACUTE PANCREATITIS developing as a complication of a surgical procedure, while generally regarded as a rare occurrence, is believed present in variable degrees following direct trauma to the pancreas. Warren reported 9 cases of acute pancreatitis which followed subtotal gastric resection, and Dunphy and his associates reported 8 cases after pancreatic injury by adjacent surgery. This postoperative complication has occured without known injury to the pancreas.

The basis for this report is a group of 22 cases of postoperative acute pancreatitis taken from the records of the Los Angeles County Hospital. A gross and microscopic postmortem examination was performed in each case.

PATHOGENESIS

There is voluminous literature, and much of it controversial, concerning the etiology of pancreatitis. Obstruction of the pancreatic ducts, spasm of the sphincter of Oddi, the reflux of bile into the pancreatic ducts via a common channel, infection, and ischemia are a few of the many factors which have been implicated.

Trauma, accidental or surgical, is added to this list of pathogenic agents. A severe blow to the abdomen, as one might expect during an automobile collision, may cause pancreatic injury by the transmission of the force to the pancreas against the vertebral column. Pancreatic contusion with edema is the result. According to Howard and Ivy and Gibbs, rupture of the ducts with liberation of enzymes and extensive necrosis may occur. Berne and Walters reported 18 such cases of acute pancreatitis from closed abdominal trauma. The accidental trauma may also be of the open penetrating variety with direct injury to the pancreas.

Surgical trauma to the pancreas occurring during an operative procedure by palpation, manipulation, mobilization, crushing or cutting, and the resultant inflammation is another factor in the pathogenesis of acute pancreatitis. During surgical procedures performed for lesions of the stomach, duodenum, sphincter of Oddi, gallbladder, and the common bile duct, the head of the pancreas is inadvertently traumatized. The small and large pancreatic ducts may be occluded by the pancreatic edema produced by the blunt injury or the entire pancreatic ductal system may be obstructed by encroachment on the termination of the pancreatic ducts, which measures on the average 0.09 centimeter in diameter, according to Sterling. Obstruction of the pancreatic ducts is widely accepted as an important cause of pancreatitis.

Schmieden and Schering found 11 of 91 cases of acute pancreatitis following gastric surgery were caused by ligation of the duct of Santorini. This duct is known to drain a large portion of the pancreas in about 10 per cent. It is vulnerable to injury since it enters the duodenum on the ventral aspect as the duct approaches the lesser papilla, nearly 2½ centimeters proximal to the papilla of Vater. The duct of Wirsung is also vulnerable by its location on the ventral surface of the pancreas, as pointed out by Cattell and Millbourn (15). Millbourn emphasized the importance of injury to the ducts in the development of acute pancreatitis (14).

Spasm of the sphincter of Oddi and of the duodenal musculature around the orifices of the pancreatic ducts may be a causative agent, as advanced by Archibald and supported by Doubilet and Mulholland. This

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obstructive mechanism is known to exist following trauma to the duodenum and sphincter of Oddi. It may be present after no apparent trauma to these parts. A common piece of supportive evidence is the large quantity of bile drainage from an indwelling T tube after choledochal exploration seen during the first 48 to 72 hours postoperatively. The drainage gradually diminishes during the next 48 hours, when only a few cubic centimeters of bile may be seen in the drainage bottle. This phenomenon is the result of spasm of the sphincter of Oddi or of the duodenal musculature.

Vascular injuries with interference of the blood supply to the pancreas have been emphasized by Popper, Millbourn, and Dunphy. The pancreas has a generous blood supply and certainly ligations of major vessels supplying the pancreas have been carried out with no injury to the organ. However, if the gastroduodenal artery is ligated during a subtotal gastric resection for a hemorrhaging duodenal ulcer, and there are also pancreatic edema from trauma and ductal obstruction, it may be that with vascular occlusion, a situation as has been demonstrated by Popper's experimental studies, occurs with acute hemorrhagic pancreatitis the result. Dunphy calls particular attention to the vulnerability of the posterior pancreaticoduodenal artery, a branch of the gastroduodenal artery.

Acute pancreatitis as a postoperative complication with no apparent pancreatic trauma is rare. Gogol and Morris reported fatal cases which followed thyroidectomy for exophthalmic goiter. Renner presented a case which followed a transurethral prostatectomy. He thought that the marked increase in proteolytic enzyme activity may be a factor. Rich and Duff thought that the release of proteolytic enzymes from the burned tissues in a 13 year old female may have caused pancreatitis. McFarlane and Biggs suggested that there is increased proteolytic enzyme activity in burns, transfusion reactions, and during operation. Ackerman reported a case of hemorrhagic pancreatitis which followed a transfusion reaction. He stated that shock occurred with atony of capillaries, plasma transudation, hemoconcentration, and slowed circulation in areas of venocapillary dilatation. Thrombosis was favored and occurred in the pancreas and in the bowel with ulceration.

Duodenal stasis, as may be seen with obstruction of the afferent loops of jejunum in a gastrojejunostomy or with postoperative adynamic obstruction, may also be a contributing factor. It could conceivably be a reservoir of infectious or chemically irritating material which could pass into the pancreatic ducts via an incompetent papilla by a reflux mechanism. The sphincter may be rendered incompetent following the removal of an impacted calculus or a sphincterotomy. Thus infection may join other factors to incite this process. The stasis, with distention of the duodenum, may also promote spasm of the sphincter of Oddi and duodenal musculature and pancreatic duct obstruction.

Rich and Duff found that sludging and thickening of pancreatic secretions might lead to functional ductal obstruction. Snyder and Lium showed that pancreatic secretions are reduced by dehydration, atropine, and ether anesthesia, factors which are present with major surgical procedures. Dunphy and his associates reported a few cases of increased viscosity of duodenal aspirations following pancreatic manipulation and palpation and suggested that this is due largely to altered pancreatic secretions following surgery. Such a change may favor obstruction in the small pancreatic ducts.

DISCUSSION

Unfortunately, it is impossible to indicate precisely the cause of the pancreatitis in these 22 postoperative cases. It is likely that factors or a combination of factors previously described have been responsible for the necrotizing process produced. Acute pancreatitis was considered the primary cause of death in 14 or 63.7 per cent.

Except in the first 4 cases listed in Table I, there was apparently direct trauma to the

TABLE I.—A TABULATION OF 22 CASES OF POSTOPERATIVE ACUTE PANCREATITIS

Case No.	*Age, Years*	*Sex*	*Procedure*	*Degree of pancreatic trauma*	*Type and degree of acute pancreatitis*		*Postoperative day of death*
			NO APPARENT TRAUMA				
1	60	M	Sigmoid colostomy	0	FN	xxx	10
2	80	F	Cecostomy	0	FN	xxx	14
3	67	M	Transurethral prostatic resection	0	FN	x	8
4	61	M	Umbilical herniorrhaphy	0	FN	xx	1
			GASTRIC SURGERY				
5	61	M	Posterior gastroenterostomy	x	FN	xxx	13
6	52	M	Gastroenterostomy, needle biopsy of pancreas	xx	FN	xxx	10
7	46	M	Subtotal gastric resection	x	FN	xx	6
8	70	M	Subtotal gastric resection and choledochostomy	xx	FN	xx	7
9	59	M	Hemorrhage from head of pancreas controlled Subtotal gastric resection	xxx	FN	xx	44
10	68	F	Ulcer freed from head of pancreas Subtotal gastric resection	xxx	HN	xx	2
11	51	M	Carcinoma resected from head of pancreas Subtotal gastric resection	xxx	SN	xxx	1
12	54	F	Ulcer resected from head of pancreas Subtotal gastric resection	x	HN	xx	6
13	69	M	Exploratory laparotomy, gastrotomy	x	HN	xx	21
			GALLBLADDER—COMMON DUCT				
14	49	F	Choledochostomy, duodenum Kocherized	xx	FN	xxx	2
15	61	M	Cholecystectomy	x	FN	xx	5
16	60	F	Cholecystectomy and choledochostomy	x	FN	xx	17
17	54	M	Cholecystectomy and choledochostomy	x	HN	xxx	8
18	78	F	Cholecystectomy and choledochostomy	x	FN	xxx	29
19	58	F	Cholecystectomy, choledochostomy, and transduodenal sphincterotomy	xx	HN	xxx	2
			PANCREATIC BIOPSY AND EXCISION				
20	71	M	Cholecystojejunostomy, biopsy of pancreas	xxx	HN	xxx	4
21	42	F	Cholecystectomy, choledochostomy, and excision of pancreatic cyst	xxx	HN	xxx	4
22	66	F	Excision of insulinoma	xxx	FN	xxx	26

0—xxx—Estimate of severity. FN—Fat necrosis.
HN—Hemorrhagic necrosis. SN—Suppurative necrosis.

pancreas. The degree of trauma varied and is not proportionate to the severity of the pancreatitis. In 4 of the 9 gastric cases there was considerable crushing and cutting trauma to the pancreas which occurred during the dissection of an ulcer or neoplasm from the head of the pancreas. The trauma was considered marked in the pancreatic biopsy and excision group of cases. Undoubtedly, many a pancreas is biopsied without acute pancreatitis complicating the procedure. The combination of etiologic factors referred to may be the answer to why some of these progress to a fatal necrotic process.

Choledochostomy was performed in 7 of these cases in conjunction with another procedure. By necessity in this group there is blunt trauma to the pancreas, duodenum, and sphincter of Oddi. Again, a combination of factors may be brought into play, such as pancreatic edema, spasm of the sphincter of Oddi and duodenal musculature, pancreatic ductal obstruction, and the introduction of infected chemically irritating gastric and duodenal secretions by instrumentation of the choledochus into the duodenum.

There was 1 fatal case of acute hemorrhagic pancreatitis which followed an elective cholecystectomy, choledochostomy, and transduodenal sphincterotomy. In this case, death occurred 44 hours after the surgical procedure. At autopsy, the necrotic pancreas was found as the primary cause of death. Blatherwick and Pattison reported 2 other cases of fatal hemorrhagic pancreatitis which followed transduodenal sphincterotomy. In one of these the long-limbed T tube

was used, as advocated by Cattell and Colcock. Smith and his associates also reported a similar case which followed sphincterotomy and use of the long-limbed T tube. In addition to several factors already implicated with such a procedure, is the reflux of duodenal contents through an incompetent sphincter of Oddi. This regurgitation is likely to occur in the postoperative patient when pancreatic secretion is at a minimum. Ascending cholangitis and hepatitis have occurred following section of the sphincter of Oddi. Inflammation of the pancreatic ducts and pancreatitis may also occur after sphincterotomy in the presence of a common channel. The long-limbed T tube may also contribute to the possible causes of pancreatitis by occluding the orifice of the main pancreatic duct or by pressure on the duct of Wirsung, where the duct, according to Sterling, is slit-like and parallel to the choledochus. In all this group of cases, there is also blunt trauma by palpation and manipulation of the pancreas.

The type of pancreatic necrosis varied. There was fat necrosis without hemorrhage in 14 of the cases, hemorrhagic necrosis in 7, and in 1 the process was suppurative and necrotic. This predominance of the fat necrotic type might be explained on the basis of a low or absent trypsin factor in the pancreatic secretion of the operative and postoperative patient. Death occurred sooner in the hemorrhagic type than in the fat necrotic group, 6.7 and 13.7 postoperative days respectively. The average length of survival in these cases was 8.3 postoperative days. Four died within 48 hours after surgery.

There was evidence of pre-existing chronic pancreatitis in 10 of the cases. An acute episode, perhaps augmented or precipitated by the emotional and physical stress of surgery, is recognized as a possibility in this group of cases. It is believed that the increased interlobular fibrosis in the chronically inflamed pancreas renders the organ more vulnerable to trauma and ductal obstruction.

From the anesthetist's operative records, 7 were found to have sustained drops (over 15 minutes) in blood pressure. The systolic determinations were below 100 millimeters of mercury and as low as 60 millimeters of mercury for varying lengths of time, as long as 2 hours. Shock has already been mentioned as a possible cause of pancreatitis. Vascular hypotension and the anoxemia produced has been known to cause liver damage. Dragstedt and his associates and Montgomery and his associates have demonstrated a relationship to exist between the liver and the pancreas. Factors, such as malnutrition, alcoholism, and certain toxic substances have been found by Stenson and his associates and Lindsay and his associates to produce lesions in the liver and pancreas concomitantly. Portal stasis with resultant poor oxygenation of pancreatic blood was cited as a possible cause of the high incidence of pancreatitis in cirrhotics. Six of the 7 patients who had vascular hypotension during surgery also had hepatic inflammatory changes. The lowered blood pressure may have been a contributing cause of pancreatitis. Five of these hypotensive patients also had chronic pancreatitis.

PROPHYLAXIS AND MANAGEMENT

In the production of postoperative pancreatitis, several etiologic factors associated with surgical operations have been discussed. These factors must be recognized and given proper consideration, especially when the procedure involves the pancreas.

The prophylactic measures are summarized to include: gentleness in the handling of the pancreas; avoidance of ductal injury and vascular occlusion when possible; the relief of expected sphincteric spasm with vagal blocking agents; overcoming vascular hypotension and dehydration promptly; avoidance of duodenal stasis; treatment of potential and active infection with broad spectral antibiotics; and the relief of postoperative pain and anxiety without the use of morphine and codeine, drugs known to promote spasm of the sphincter of Oddi.

Popper and Necheles (19), using dogs, found that pancreatic injury caused inhibi-

tion of pancreatic secretion during the immediate postoperative period. Pancreatic wounds healed and ducts sealed during this period. They concluded that stimulation of the pancreas should be avoided after pancreatic biopsies and surgical injuries. Thistlewaite found experimentally that anticholinergic drugs reduced the volume and amylase content of pancreatic secretion by 20 per cent.

When pancreatic biopsy or excision is indicated, the utilization of all preventive measures as well as drainage of the biopsy site and peritoneal cavity is encouraged. The drain may serve as an aid in diagnosis. It may also help remove enzymatic necrotizing juices and large quantities of peritoneal fluid which occasionally collect with acute pancreatitis.

Only 4 of the 22 cases were recognized as having acute pancreatitis during the postoperative course. It is worth while to be suspicious and anticipate the complication, especially when there has been pancreatic trauma. A test for hyperamylasemia and a urinary diastase determination are indicated 24 and 48 hours after surgery or when there are unexplainable abdominal signs and symptoms. Perryman and Hoerr found a significant postoperative rise of the serum amylase in 27 or 32 per cent of 85 unselected patients undergoing surgery. The highest incidence of elevations occurred after gastric resection and after common duct exploration, 47 and 35 per cent respectively.

With a diagnosis of postoperative acute pancreatitis established on laboratory and clinical findings, the complication must be managed with continuous nasogastric suction, parenteral fluid and electrolyte replacement, a vagal blocking agent, and an antibiotic of broad spectral coverage.

CONCLUSION

The pathogenesis of acute pancreatitis has been reviewed with etiologic factors associated with surgery considered. Twenty-two cases of postoperative acute pancreatitis were presented. The lethal process occurs occasionally following surgical pancreatic trauma and rarely after surgery with no apparent trauma to the pancreas. Measures to prevent and manage the complication have been discussed.

REFERENCES

1. Ackerman, L. V. Acute pancreatitis following blood transfusion. Arch. Path., Chic., 1942, 34: 1065–1069.
2. Archibald, E. Experimental production of pancreatitis in animals as a result of the resistance of the common ducts phincter. Surg. Gyn. Obst., 1919, 28: 529–545.
3. Berne, C. J., and Walters, R. L. Traumatic pancreatitis. California M., 1953, 79: 279–281.
4. Blatherwick, N. H., and Pattison, A. C. Acute pancreatitis complicating choledochal sphincterotomy. Am. J. Surg., 1954, 88: 129–135.
5. Cattell, R. B. Anastomosis of duct of Wirsung; its use in palliative operations for cancer of head of pancreas. Surg. Clin. N. America, 1947, 27: 636–643.
6. Doubilet, H., and Mulholland, J. Etiology and treatment of pancreatitis. N. York State J. M., 1949, 49: 2938–2944.
7. Dragstedt, L. R., Van Prohaska, J., and Harms, H. P. Observations on substance in pancreas (fat metabolizing hormone) which permits survival and prevents liver changes in depancreatized dogs. Am. J. Physiol., 1936, 117: 175–181.
8. Dunphy, J. E., Brooks, J. R., and Achroyd, F. Acute postoperative pancreatitis. N. England J. M., 1953, 248: 445–451.
9. Gogol, L. J. Hemorrhagic pancreatitis following thyroidectomy. California M., 1937, 47: 255.
10. Howard, J. M. Surgical physiology of pancreatitis. Surg. Clin. N. America, 1949, 29: 1789–1800.
11. Ivy, A. C., and Gibbs, G. E. Pancreatitis: review. Surgery, 1952, 31: 614–642.
12. Lindsay, S., Etenman, C., and Chaikoff, I. L. Pancreatitis accompanying hepatic disease in dog fed a high fat, low protein diet. Arch. Path., Chic., 1948, 45: 635–638.
13. McFarlane, R. G., and Biggs, R. Fibrinolysis: its mechanism and significance. Blood, N. Y., 1948, 3: 1167–1187.
14. Millbourn, E. On acute pancreatic affections following gastric resection for ulcer or cancer and the possibilities of avoiding them. Acta chir. scand., 1949, 98: 1–21.
15. Idem. On excretory ducts of pancreas in man, with special reference to their relations to each other, to common bile duct and to duodenum. Acta anat., Basel, 1950, 9: 1–34.
16. Montgomery, M. L., Entenman, C., Gibbs, G. E., and Chaikoff, I. L. Influence of ingestion of pancreatic juice upon liver fat in depancreatized dog maintained with insulin. Proc. Soc. Exp. Biol., N. Y., 1940, 43: 349–351.
17. Morris, W. R. Pancreatic fat necrosis following subtotal thyroidectomy. J. Am. M. Ass., 1953, 100: 1954.
18. Perryman, R. G., and Hoerr, S. O. Observations on postoperative pancreatitis and postoperative elevation of the serum amylase. Am. J. Surg., 1954, 88: 417–420.
19. Popper, H. L., and Necheles, H. Pancreatic injuries; an experimental study. Surg. Gyn. Obst., 1951, 93: 621–624.

20. Popper, H. L., Necheles, H., and Russell, K. C. Transition of pancreatic edema into pancreatic necrosis. Surg. Gyn. Obst., 1948, 87: 79–82.
21. Renner, W. F. Postoperative acute pancreatitis and lower nephron syndrome. J. Am. M. Ass., 1951, 147: 1654–1655.
22. Rich, A. R., and Duff, G. L. Experimental and pathological studies on pathogenesis of acute hemorrhagic pancreatitis. Bull. Johns Hopkins Hosp., 1946, 58: 212–259.
23. Schmeiden, V., and Schering, W. Surgery of the pancreas with especial consideration of acute pancreatic necrosis. Surg. Gyn. Obst., 1928, 46: 735–751.
24. Smith, S. W., Barker, W. F., and Kaplan, L. Acute pancreatitis following transampullary biliary drainage. Surgery, 1951, 30: 695–700.
25. Snyder, W. H., Jr., and Lium, R. Pancreatic fistula. Surg. Gyn. Obst., 1936, 62: 57–64.
26. Stenson, J. C., Jr., Baggenstoss, A. H., and Morlock, C. G. Pancreatic lesions associated with cirrhosis of the liver. Am. J. Clin. Path., 1952, 22: 117–125.
27. Sterling, J. A. The common channel for bile and pancreatic ducts. Surg. Gyn. Obst., 1954, 98: 420–424.
28. Thistlewaite, J. R. Study of the effect of banthine, vagotomy, and subtotal gastric resection upon pancreatic secretion. Surg. Gyn. Obst., 1951, 93: 616.
29. Warren, K. W. Acute pancreatitis and pancreatic injuries following subtotal gastrectomy. Surgery, 1951, 29: 643–657.

ACUTE CHOLECYSTITIS FOLLOWING THE SURGICAL TREATMENT OF UNRELATED DISEASE

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IT IS NOW RECOGNIZED that it is more than mere coincidence that acute cholecystitis may develop in the early postoperative period following surgical treatment of unrelated disease. However, only sporadic case reports were available until 1947 when 17 cases occurring in this center between September 1, 1932 and September 1, 1946 were reported (3). Since then others have reported their findings in cases of acute cholecystitis which occurred postoperatively. Sparkman in 1952 reported 5 proved cases, and Schwegman in 1953 reviewed the findings in 17 cases observed in a 23 year period. Table I lists these available reports.

The present study is an analysis of 18 proved cases occurring between September 1, 1946 and June 30, 1955 on the surgical pavilions of The New York Hospital. The purpose of the investigation was to determine the features of acute cholecystitis when it occurs in the postoperative period and to evaluate our experience in its management.

CLINICAL MATERIAL

Age and sex. The age of the patients varied from 25 to 78 years. The average age was 60.7 years. Significantly, all but 2 of the patients were over 50 years of age. Six patients were in their sixth decade and 6 (all males) were 70 years of age or older.

Neither sex predominated. There were 9 males and 9 females. The average age of the males was 65.9 years, and the average age of the females was 55.5 years.

Primary disease and operation. The primary diagnosis included a great variety of diseases. Similarly a variety of operations were performed. No particular disease was the more common though several occurred more than once. Appendicitis in one form or another and carcinoma of the colon both occurred 4 times. The 2 patients under the age of 50 years both had acute appendicitis; in 1 case the appendix was perforated. There were also 2 cases of prostatic hypertrophy, carcinoma of the face, and pyelonephritis. The remaining diagnoses included varicose veins, cataract, retinal detachment, and inguinal hernia. Infection was associated with the primary disease in 6 patients.

Appendectomy was performed in 3 instances and a colectomy in 4; of these 3 were right hemicolectomies. A transurethral prostatectomy was performed in 2 cases. In addition, there were 2 operations upon the kidney, eye, and face. For one reason or another an operation was performed on the colon and appendix in almost half of the patients.

In 4 instances complications developed after the primary operation. Severe sepsis due to peritonitis occurred after appendectomy with drainage for a gangrenous and perforated acute appendicitis (Case 1). This was the only patient in whom acute cholecystitis apparently developed in a gallbladder without calculi or an underlying chronic inflammation. The organisms cultured from the peritoneal exudate were the same as those cultured from the contents of the gallbladder. A wound infection complicated 3 cases; in addition, uremia was present in 1 instance. In these cases the interval of time between the wound infection and acute cholecystitis was 7 to 10 days. In Case 11 the wound infection was minimal. However, Staphylococcus aureus hemolyticus was cultured from both the wound and the gallbladder. In Case 13 the postoperative course

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TABLE I.—POSTOPERATIVE ACUTE CHOLECYSTITIS

Author and reference No.	*No. of cases*
Duncan (1)	1
Kocker and Matti (8)	1
Vest (12)	1
Fisher (2). Quoted by Vest (12)	1
Glenn (3)	17
Graham (6). Discussion of report by Glenn (3)	1
Sparkman (11)	5
Schwegman and DeMuth (10)	17
Glenn and Wantz, 1955	18
Total	62

was stormy. Escherichia coli and Clostridium welchii were cultured from the wound yet there was no growth from the contents of the gallbladder. In Case 15 uremia and a severe wound infection were coexistent. Staphylococci and streptococci were cultured from the wound while Escherichia coli was demonstrated in an empyema of the gallbladder. The majority of the patients following the primary operation had some elevation of temperature. It was marked, however, in only 2 patients (Cases 1 and 13).

In general the primary diseases were those commonly seen in older patients and for the most part seemed to have little relation to the acute cholecystitis. This also seemed true for the operation per se. The development of acute cholecystitis, as is pointed out later, is related to the operation chiefly in the fact that it induces a period of fasting. Complications of the primary disease or operation may be of significance, however, if they produce an acute systemic disease.

Biliary tract disease. During the initial evaluation of these patients in the hospital the past history gave evidence in 10 instances of long-standing biliary tract disease. In 9 of these patients gallstones were known to be present and were demonstrated either by cholecystogram or during abdominal exploration at a previous operation. Indeed most of them for years had consulted physicians frequently for relief of their symptoms and in 1 patient (Case 9) a cholecystostomy had been performed 10 years previously for acute cholecystitis.

There were 8 patients without symptoms suggesting biliary tract disease. However, in 2 of these patients (Cases 5 and 6) it was noted at the primary operation that chronic cholecystitis was present as manifested by a scarred and contracted gallbladder but without evident calculi. Thus biliary tract disease was believed to exist in two-thirds of the patients. A history of previous biliary tract disease unquestionably served as an aid in the recognition of acute cholecystitis.

Fasting and the resumption of food ingestion. All the patients fasted. The duration of the fast varied from 1 to 17 days depending upon the nature of the disease, preoperative preparation, operation, and the postoperative course. Thirteen patients fasted 3 or more days, with an average of 9.4 days while 5 fasted only the day of the operation. Hydration of these patients seemed adequate with 1 exception (Case 13) during the fasting period.

The interval between the resumption of food ingestion and the development of the signs and symptoms of acute cholecystitis varied from 1 to 18 days. In 10 patients acute cholecystitis developed within the first 24 hours after the resumption of oral food. In 8 cases the interval between the termination of the fast and the recognition of signs and symptoms of acute cholecystitis varied from 2 to 18 days.

An obvious inverse relationship exists between these two time intervals if they are compared. In general the signs and symptoms of acute cholecystitis occurred shortly after the resumption of oral food when fasting was prolonged. In fact, a few patients developed pain within minutes after first eating. This sequence of events was evident in 66.6 per cent of the cases.

There were unusual features in those patients in whom this sequence of events was not quite as evident. In 2 patients (Cases 14 and 15) fasting lasted only the day of the operation and the acute cholecystitis was not evident for days after first taking food. However, both these patients, asymptomatic before operation, complained constantly after the operation of vague epigastric pain and indigestion. Their symptoms may very likely have been due to minimal acute cholecys-

TABLE II.—DATA ON 18 PATIENTS DEVELOPING ACUTE CHOLECYSTITIS FOLLOWING OPERATION THE NEW YORK HOSPITAL—CORNELL MEDICAL CENTER, SEPTEMBER 1, 1946 TO JUNE 30, 1955

Case No.	*Age, years*	*Sex*	*History of biliary tract disease*	*Diagnosis*	*Operation*	*Complication*	*Duration of fast, days*	*Days between fast and onset of symptoms*	*Postoperative day onset of symptoms*
1.....	25	M	—	Gangrenous appendix with perforation	Appendectomy	Peritonitis	11	No food taken	10
2.....	25	F	+	Acute appendicitis	Appendectomy	None	3	1	2
3.....	68	F	—	Acute appendicitis	Appendectomy	None	6	1	6
4.....	68	F	+	Chronic appendiceal abscess	Colectomy, rt.	None	14	1	10
5.....	78	M	—	Carcinoma cecum	Colectomy, rt.	None	11	1	8
6.....	78	M	—	Carcinoma colon, rt.	Colectomy, rt.	None	17	1	9
7.....	73	M	+	Carcinoma of face	Division of pedicle flap	None	1	1	2
8.....	75	M	—	Carcinoma of face	Skin graft to face	None	11	1	11
9.....	74	M	+	Cataract	Cataract extraction	None	1	1	2
10.....	65	F	—	Inguinal hernia	Hernioplasty	None	3	1	3
11.....	61	F	+	Carcinoma of sigmoid	Closure of colostomy	Wound infection	17	2	14
12.....	71	M	+	Prostatic hypertrophy	Transurethral prostatectomy	None	4	1	3
13.....	50	F	+	Carcinoma of sigmoid	Sigmoidectomy	Wound infection	13	5	18
14.....	61	F	+	Pyelonephritis	Ureteroplasty	None	1	18	18
15.....	54	M	—	Pyelonephritis	Nephrotomy	Uremia. Wound infect.	3	15	17
16.....	51	F	—	Varicose veins	Phlebectomy	None	1	4	5
17.....	52	F	+	Retinal detachment	Retinal re-attachment	None	1	13	13
18.....	65	M	+	Prostatic hypertrophy	Transurethral prostatectomy	None	1	7	7

titis. Another 2 patients (Cases 17 and 18) were able to associate the symptoms specifically to ingestion of a fatty food. In addition, 1 patient (Case 17) was confined to a strict supine position in bed following diathermy for retinal reattachment. The association of uremia and acute cholecystitis is well known and occurred in 1 patient (Case 15). In addition this patient was taking a low fat diet, actually, only quite sparingly. In Case 13, summarized later, there is an association with the resumption of oral food though not obvious at first glance.

The postoperative day on which acute cholecystitis developed varied from 2 to 18. No particular period during the postoperative course is demonstrated as is frequently seen with such complications as phlebitis and wound infections. Rather the postoperative day that it occurs seems dependent upon both the duration of fasting and the nature of the food ingested.

Drugs. All the patients received at one time or another during hospitalization for operation either morphine, codeine, or demerol for the relief of pain and sedation. Eleven patients received one of these drugs within a day prior to the recognition of the acute cholecystitis. Six patients did not receive any for several days prior to the evidence of acute cholecystitis. There was no specific correlation between the nature and quantity of narcotic drugs and the development of acute cholecystitis. This group of patients was observed within the antibiotic era. Sixteen patients were receiving antibiotics when the acute cholecystitis developed. As might be expected this treatment did not seem to alter the clinical picture or subsequent course of the acute cholecystitis.

Treatment. Ten, or 55.5 per cent, of the patients underwent cholecystectomy. Their average age was 54.7 years, and the oldest patient was 75 years of age. All recovered without complications. Cholecystostomy was performed in the remaining 8 cases (44.5 per cent) either because of the condition of the patient, the nature of reaction about the

gallbladder, or because of the technical problems confronting the operator that precluded the more complete procedure. The average age of these patients was 68.3 years.

Pathology. In 1 patient acute cholecystitis occurred in a gallbladder without evidence of pre-existing disease and without calculi. In the remaining 17 cases acute inflammation of various degrees was believed to be superimposed on the chronically inflamed gallbladder. Twelve were considered by the pathologist merely to represent an acute exacerbation of a chronic cholecystitis. Calculi were not found in 3 of these cases. Calculi were present in the gallbladders of the remaining patients, in 3 of which areas of localized gangrene were present and 1 was wholly gangrenous. There was 1 instance of empyema. Fortunately, none of the gallbladders had perforated. In all there were 4 cases of noncalculous acute cholecystitis, an incidence of 22.2 per cent.

The contents of the gallbladders were described as "milky white or green" in 8 cases, and in 9 cases, as thick, tenacious, viscid, or dark green, brown, or tarry. It may be significant that the cases of noncalculous acute cholecystitis were in this latter group.

Cultures were made in 16 cases. In 7 of these the contents of the gallbladder were sterile. The cultures grew a variety of organisms in the remaining 9 cases. Escherichia coli was most frequently noted, but Bacillus pyocyaneus, Aerobacter aerogenes, Streptococcus hemolyticus, and Staphylococcus aureus were also found. With the exception of Case 1 and possibly Case 11, coexistent systemic clinical infection bore no relation to the pathology. Except for the less common presence of gallstones the morbid anatomy of acute cholecystitis appears the same whether or not it occurs postoperatively. We believe we should stress the fact that we were unable to establish a correlation between the pathologic findings (degree of acute inflammation) and the clinical manifestations of acute cholecystitis, such as the duration of the preceding fasting period and the duration, intensity, and severity of the signs and symptoms.

RESULTS

There was 1 death, a mortality of 5.55 per cent. This occurred in a 50 year old woman (Case 13, no autopsy) and was attributed to coronary occlusion. A summary of this case is given as illustrative of a common course of events.

DISCUSSION

Acute cholecystitis occurring after operative treatment for unrelated disease appears to be a complication affecting primarily aged patients and favoring neither sex. Similar conclusions were reached in earlier reports. The predominance in aged patients is indicated by the fact that 88.9 per cent of the patients in this study were over 50 years of age. In fact, 50 per cent were over 65 years of age. This is important as the mortality and morbidity of acute cholecystitis increase abruptly with advancing years, not only because attendant jeopardizing systemic diseases are more prevalent but because of the greater incidence of complications, particularly perforation with its high mortality. Our experience indicates that 50 per cent of the deaths following acute cholecystitis in aged patients could be attributed to the effects of perforation.

The fact that each year the proportion of patients in the aged group undergoing operation becomes greater and that with advancing years the incidence of biliary tract disease also rises probably accounts for the increasing frequent occurrence in this center. For example in the 14 years from 1932 to 1946 there were 17 cases observed, while 18 cases were observed in the 9 year period of this study. It may be expected then that as life expectancy is prolonged this complication will become increasingly common unless, of course, biliary tract disease is interrupted at an earlier age.

The relative high proportion of males as opposed to females with postoperative acute cholecystitis is contrary to the predominance of females with acute cholecystitis, as usually encountered. However, we would call attention to the fact that the average age of the

TABLE III.—PATHOLOGY

Case No.	*Sedation*	*Treatment*	*Inflammation*	*Appearance of contents*	*Stones*	*Culture*	*Survival*
1.....	0	Cholecystectomy	Acute cholecystitis	Tenacious brown	0	0	Yes
2.....	+	Cholecystectomy	Acute exacerbation of chronic cholecystitis	Purulent viscid green	+	?	Yes
3.....	0	Cholecystectomy	Acute exacerbation of chronic cholecystitis	Viscid dark green	+	—	Yes
4.....	+	Cholecystectomy	Acute exacerbation of chronic cholecystitis	Viscid dark green	+	—	Yes
5.....	0	Cholecystostomy	Acute exacerbation of chronic cholecystitis	Thick purulent bile	0	+	Yes
6.....	0	Cholecystostomy	Acute exacerbation of chronic cholecystitis	Black, tarry	0	+	Yes
7.....	+	Cholecystostomy	Acute exacerbation of chronic cholecystitis	Milky yellow	+	+	Yes
8.....	0	Cholecystectomy	Acute exacerbation of chronic cholecystitis	Milky white	+	+	Yes
9.....	+	Cholecystostomy	Acute exacerbation of chronic cholecystitis	Muddy dark green	0	?	Yes
10.....	+	Cholecystectomy	Localized area gangrene acute exacerbation of chronic cholecystitis	Thin milky yellow	+	+	Yes
11.....	+	Cholecystectomy	Acute exacerbation of chronic cholecystitis	Milky white	+	+	Yes
12.....	+	Cholecystostomy	Acute exacerbation of chronic cholecystitis	Milky yellow	+	+	Yes
13.....	0	Cholecystectomy	Localized area gangrene acute exacerbation of chronic cholecystitis	Milky white	+	—	No
14.....	+	Cholecystectomy	Acute exacerbation of chronic cholecystitis	Milky green	+	—	Yes
15.....	+	Cholecystostomy	Acute exacerbation of chr. cholecystitis. Empyema	Pus	+	+	Yes
16.....	+	Cholecystectomy	Diffuse gangrene	Dark red green	+	—	Yes
17.....	0	Cholecystectomy	Acute exacerbation of chronic cholecystitis	Milky yellow	+	—	Yes
18.....	+	Cholecystectomy	Localized areas gangrene acute exacerbation of chronic cholecystitis	Tenacious dark brown	+	—	Yes

males was 10 years greater than that of the females. Actually the only patients over 70 years of age were males. Mueller-Deham and Rabson citing 1,000 consecutive autopsies reported that in early adult life gallstones were 7 times more frequent in females, but that with advancing years the incidence becomes nearly equal in the two sexes and that after 70 years of age more than 50 per cent had cholelithiasis. Therefore, this marked increased incidence of biliary tract disease in males of advanced years possibly explains the high proportion of males with postoperative acute cholecystitis.

The pathogenesis of acute cholecystitis is not clearly understood. The causative factors in pathogenesis of acute cholecystitis occurring postoperatively are probably ultimately the same as those in acute cholecystitis unrelated to surgical procedures. There are, however, several unusual features of acute cholecystitis when it occurs postoperatively suggesting that the significance of the various causative factors may be different.

In general, acute cholecystitis appears to be merely a phase of long-standing biliary tract disease and more often than not associated with cholelithiasis. In this center only 7 per cent of all cases of acute cholecystitis were without stones. However, the incidence of noncalculous acute cholecystitis developing postoperatively in this series was 22.2 per cent. Schwegman reported that 35 per cent of his cases were noncalculous. This apparent higher incidence may not be actual since many of these patients (all of Schwegman's cases) underwent cholecystostomies. In such a case a solitary small calculus impacted in the cystic duct may go unrecognized. Sometimes, it may be, however, that calculi are incidental and not involved in the genesis of acute cholecystitis developing postoperatively.

The marked predominance of its occurrence in older patients suggests that associated degenerative diseases and diminished physiologic responses may be important in its pathogenesis. Other causative factors such as uremia and systemic infection and limited activity are also apparent. The association of acute cholecystitis with uremia and acute systemic diseases is well documented. Examples of each (Cases 1 and 15) occurred in this study.

The unique event in postoperative acute cholecystitis is its developmental relationship to the resumption of oral feedings after a variable period of fasting. This fact has been emphasized before. Forceful attempts at emptying the gallbladder induced by the ingestion of food after a period of rest that occurs during fasting is, we believe, the crux in the pathogenesis of acute cholecystitis, when it develops after an operation. It is one or both of these events that provides the optimum conditions for the gallbladder to become acutely involved.

The most potent stimulus to produce contractions of the gallbladder so as to release its contents is cholecystokinin. This hormone is produced by the intestinal mucosa in the presence of fat and to a lesser degree by protein and carbohydrate. Consequently during fasting the gallbladder is not stimulated to release its contents. Accumulation, concentration, stagnation, and distention may occur. Bile production continues though diminished during fasting and, if it reaches the gallbladder, will be conserved by concentration. Viscosity is further increased by the secretion of mucin by the gallbladder. Fever, dehydration, and drugs such as morphine, demerol, and codeine which have a spasmogenic effect on the sphincter of Oddi and a relaxant effect on the gallbladder would seem to augment this process.

The viscid, stagnated contents of the gallbladder, possibly containing a high concentration of bile salts, may not readily pass through the cystic duct and thus produce a functional obstruction. Contractions of the gallbladder may not be forceful enough to express such contents through a tortuous and small cystic duct. Of course if calculi are present the likelihood of frank and unequivocal cystic duct obstruction is always imminent. The postoperative patient, reluctant to get up, tends to spend most of his time supine and quiet in bed. If fasting, the patient may be forced to maintain this position while receiving intravenous infusions. Gallstones may also gravitate to the ampulla where they may obstruct the outflow through the cystic duct or be forced into it by contractions of the gallbladder.

The forceful attempt of the gallbladder to empty its contents, particularly when stones are present, may compromise the vascular supply by compressing the lymphatics, channels, and veins. Edema develops and later the arterial supply is diminished. A viscous cycle develops, the end result of which may include infarction and necrosis. Distention alone, if marked, may lead to vascular ischemia.

This series of events creates a gallbladder which is then susceptible to bacterial invasion or the deleterious effects of toxins, enzymes, and irritating chemical agents (e.g., pancreatic secretion, bile salts, nitrogenous wastes). The rate of development and the degree of inflammation of acute cholecystitis are dependent then on the intensity of the various causative factors. Generally the manifestations of the disease are evident within a matter of hours, however, there are instances when it may take several hours.

The pathologic findings in the gallbladder of a patient who develops acute cholecystitis following an operation for unrelated disease are indistinguishable from those usually seen. To predict the degree of inflammation, or if the gallbladder is likely to perforate is impossible since the correlation between the clinical manifestations and the morbid anatomy is notoriously lacking. This is especially true in aged patients as their clinical findings are often minimal. This fact should be constantly borne in mind for it is perforation of the gallbladder in acute cholecystitis, as in appendicitis, that accounts for the major portion of the fatalities.

The clinical manifestations of pain, tenderness, right upper quadrant mass, fever, and leucocytosis make up the classical picture but all are not essential to establish a diagnosis of acute cholecystitis. A past history compatible or indicative of biliary tract disease serves frequently as an aid in diagnosis. If such is the case cholecystograms are advisable during the initial evaluation of the patient. There may be occasions when the effects of the primary disease or operation may confuse or delay diagnosis. Occasionally acute cholecystitis may mimic other diseases and conditions such as coronary occlusion, pancreatitis, hiatus hernia, and the complications of diverticulosis. Awareness of the possibility of acute cholecystitis will often prevent an incorrect diagnosis. We have employed intravenous cholangiography and cholecystography as an aid in establishing a correct diagnosis. Such significant information made available within an hour or two justifies the procedure.

The treatment of acute cholecystitis we believe is early surgical intervention. By early surgery we do not mean that the patient is rushed immediately to the operating room. Rather we mean that the patient is first prepared carefully and is in optimal condition for either cholecystectomy or cholecystostomy. Of course there should be no other contraindication to operation. Our experience in the past 22 years[1] with 850 patients with acute cholecystitis at The New York Hospital—Cornell Medical Center justifies early surgical treatment (4). We think this approach particularly applicable for those who develop postoperative acute cholecystitis with its predominance in aged patients. In the young adult the risk of nonsurgical treatment is much less. However, in older patients the risk of nonsurgical treatment is much greater.

The mortality rate of 5.55 per cent in this series of patients 88 per cent of whom were over the age of 50 years is favorable and is comparable to our experience in the treatment of acute cholecystitis in general (4, 5). Equally important was the fact that the incidence of complications was also low. Hospitalization in none of these patients was consequently extensively prolonged.

Cholecystectomy was performed in the majority of these cases. It represents the ideal therapy as it not only eradicates the dangers of the immediate process but relieves the patient of the discomforts and hazards of continued biliary tract disease.

However, elderly patients who have recently undergone a major operation may not always be suitable candidates for cholecystectomy. In addition in some patients the technical hazards may preclude a more complete procedure. It is in this group of patients that we believe a cholecystostomy should be performed. It is a lesser procedure readily performed under local anesthesia. In such patients cholecystostomy may be life-saving in that it averts the immediate dangers of the complications of acute cholecystitis.

For those patients who have had a cholecystostomy we believe a cholecystectomy should be done within the following 6 months when it may be undertaken under optimum circumstances. We base this recommendation upon our experience with a group of 103 patients with nonmalignant disease of the biliary tract who for one reason or another had undergone a cholecystostomy.[2] Cholecystostomy was employed in 2 to 4 per cent of the total number of biliary tract procedures each year, and in 13 to 17 per cent of the patients with acute cholecystitis. This relative constancy of its employment was not appreciably influenced by the extensive use of antibiotics, or other therapeutic advances of the past 20 years.

Only approximately 10 per cent of these patients returned to the hospital for elective cholecystectomy. Of the remaining 90 per cent, the patients without subsequent elective cholecystectomy, approximately 25 per cent required emergency operative intervention for recurrent biliary tract disease, and

[1]This period extends from September 1, 1932 to September 1, 1954.

[2]These patients were operated upon on the pavilion services of The New York Hospital—Cornell Medical Center from September 1, 1932 to September 1, 1951.

an additional 40 per cent had chronic debilitating symptoms of biliary tract origin.

In patients in whom the life expectancy is less than 2 years (malignancy with dissemination, cirrhosis with bleeding varices) there is little likelihood of biliary tract disease playing a significant role in their course and elective cholecystectomy seems unnecessary.

CASE 13. A female, 50 years of age, was admitted on May 1, 1947, with a diagnosis of carcinoma of the sigmoid. Her past history indicated long-standing biliary tract disease. Partial obstruction of the colon developed during initial evaluation and a transverse colostomy was performed under general anesthesia on May 8, 1947. At this time the gallbladder was noted to be small and contracted with a thick wall. It contained many calculi. Shortly thereafter auricular fibrillation developed and cardiac decompression followed for which digitalis was employed to control. A persistent and unexplained fever (39.3 degrees C.) with occasional chills was present for over 3 weeks.

On June 3, 1947, sigmoidectomy for carcinoma was performed under general anesthesia. Her course after this operation was particularly stormy and again febrile. It was necessary to continue nasogastric suction for 10 days to prevent vomiting which became a serious problem and was never adequately explained. On 1 occasion hypochloremic alkalosis developed when the gastric suction was prematurely discontinued. Large quantities of intravenous replacement fluid confined the patient to bed. Indiscriminately morphine, demerol, and codeine were liberally given.

On the seventh postoperative day a wound infection was evident. This was limited to the subcutaneous tissues. Culture of the exudate grew Bacillus proteus and Clostridium welchii. Penicillin was administered throughout the postoperative course. Fever was marked (39.2 degrees C.) but finally returned to normal by the fifteenth postoperative day.

On the thirteenth postoperative day a soft, low in fat diet was begun, the patient having fasted until this time. She persistently complained about the food and ate sparingly. She improved slowly for 5 days. Then suddenly, 18 days after her primary operation, she was seized with severe epigastric pain, nausea, and vomiting. There was mild epigastric tenderness. Her temperature rose abruptly to 39.4 degrees C. and her white blood count was 17,500. The patient was given nothing by mouth and then clear fluids supplemented by infusions for the next 5 days. Her symptoms abated, and her temperature returned to normal. Again she was given food. This was followed by an exacerbation of her pain, nausea, and vomiting. Her temperature again rose to 38 degrees C. and a tender mass was palpable in the right upper quadrant.

On June 27, 1947, a cholecystostomy was performed under local anesthesia. The gallbladder was acutely inflamed. There were localized areas of gangrene. There was no obvious perforation evident. Contents of the gallbladder were milky white, viscid, and sterile on culture. This procedure was tolerated well and she seemed to be better until the third postoperative day. Then suddenly she complained of severe precardial and substernal pain and within minutes expired. Coronary occlusion was assumed to be the cause of death, though autopsy was not performed.

The remaining 17 patients recovered uneventfully. There were no major complications. The fate of those patients undergoing cholecystostomy is important, since this operation is a compromising procedure directed at averting the immediate dangers of acute cholecystitis. Of the 8 patients undergoing cholecystostomy there was 1 death. Three patients (Cases 5, 12, and 15) underwent elective cholecystectomy within 10 months. It is too recent to evaluate the results in Case 6, now only a few weeks postcholecystectomy. One patient (Case 7) died as a result of metastatic carcinoma of the face within 2 years. Of importance, however, is the fact that one patient (Case 9) having previously undergone cholecystostomy for acute cholecystitis, underwent an emergency cholecystectomy 1 year later for a third episode of acute cholecystitis.

SUMMARY

The occurrence of acute cholecystitis in the early postoperative period of 18 patients undergoing operative treatment for unrelated disease is not fortuitous. It is prone to occur in aged patients, especially males. The unusual features are the high incidence of noncalculous gallbladders and the developmental relationship to the resumption of oral food preceded by fasting. The operation and condition for which it was done, if there is no associated acute systemic disease, are important only in so far as they provide a period of fasting.

We are interested in ways and means of attempting to prevent acute cholecystitis following the surgical treatment of unrelated disease for it may be a serious complication

particularly in those patients who are in the older age group. For those individuals known to have cholelithiasis, surgical therapy soon after the diagnosis has been established and at an early age when the morbidity and mortality are minimal provides the best method of interrupting biliary tract disease and obviating acute cholecystitis following unrelated operations. The fulfillment of such a concept is of course impractical for many patients. Our next best approach then includes prophylactic measures and should be directed at preventing the accumulation of large amounts of concentrated bile in the gallbladder and then a sudden and vigorous attempt to empty itself. Prolonged periods of fasting should be avoided whenever possible. Early mobilization after operation aids in the re-establishment of normal intestinal function. Drugs that retard bile flow from the gallbladder to the duodenum should be used with understanding and caution. Associated acute systemic disease and infection should be vigorously combatted. The resumption of oral food after an operation should be begun by giving small amounts of food, low in fat and cholesterol. For example, a coddled egg so frequently given to a postoperative patient is often the offending agent.

Cholecystectomy is the treatment of choice, though cholecystostomy may be indicated in the best interests of some patients. If cholecystostomy is performed, it should be followed within a few months by cholecystectomy if the life expectancy of the patient is over 2 years.

REFERENCES

1. DUNCAN, J. Femoral hernia; gangrene of the gall bladder; extravasation of bile; peritonitis; death. North. J. Med., 1844–1845, 2: 151–153.
2. FISHER, W. A. Quoted by S. A. Vest, Jr., (12). Internat. Surg. Digest, 1933, 15: 131–160.
3. GLENN, F. Acute cholecystitis following the surgical treatment of unrelated disease. Ann. Surg., 1947, 126: 411–420.
4. Idem. The surgical treatment of acute cholecystitis. Surg. Gyn. Obst., 1950, 90: 643–648.
5. GLENN, F., and HAYS, D. M. The age factor involved in the mortality rate of patients undergoing surgery of the biliary tract. Surg. Gyn. Obst., 1955, 100: 11–18.
6. GRAHAM, H. F. Discussion of report by Glenn, F., (3). Acute cholecystitis following the surgical treatment of unrelated disease. Ann. Surg., 1947, 126: 411–420.
7. HAYS, D. M., and GLENN, F. The fate of the cholecystostomy patient. J. Am. Geriat. Soc., 1955, 3: 21–29.
8. KOCKER, T., and MATTI, H. Ueber 100 Operationen an den Gallen wegen mit Berucksichtigung der Davenerfolge. Arch. klin. chir., 1906, 81: 655.
9. MUELLER-DEHAM, A., and RABSON, S. M. Internal Medicine in Old Age. Baltimore: The Williams & Wilkins Co., 1942.
10. SCHWEGMAN, C. W., and DEMUTH, W. E., JR. Development of acute cholecystitis following surgical treatment for unrelated disease. Surg. Gyn. Obst., 1953, 97: 167–172.
11. SPARKMAN, R. S. Abdominal emergencies following unrelated surgical procedures. Ann. Surg., 1952, 135: 863–874.
12. VEST, S. A., JR. Gangrene of the gall bladder. Internat. Surg. Digest, 1933, 15: 131–160.

PARENTERAL CALORIES FROM A SYNTHETIC WATER SOLUBLE FAT

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THE OBSERVATION that an adequate caloric intake is necessary to maintain weight and health and nitrogen balance is not new. Fat and carbohydrate were known to "spare" protein in the fasting state. Still, the full awareness of this relationship between caloric intake and protein metabolism did not assume importance until recently when clinical attention was directed toward protein metabolism with especial reference to the abnormal protein losses which occur during operations and illness. Protein depletion lowered resistance to infection, produced edema, and delayed recovery from disease. A favorable nitrogen balance was seen as one step toward recuperation. Nutritional rehabilitation accelerated a return of strength and the healing of wounds. The nutritional and metabolic aspects of disease, injury, and even bed rest came under careful scrutiny. Negative nitrogen balance which results from stress and is mediated via the pituitary adrenal axis is not amenable to therapy, and some questioned the advisability of treating a loss of this nature. Postoperative nitrogen losses can be reduced if sufficient calories are given. When attention was directed toward restitution of a favorable nitrogen balance during nutritional repletion, it became evident that the status of protein balance was most often a reflection of the caloric intake. Keys (6) found that calories were of primary importance in restoration of nitrogen balance in starved normal subjects.

The principles which apply to nitrogen balance are no different when an individual must be maintained parenterally. The problems involved are how much can be given intravenously and what should take precedence. An analogous problem in nitrogen balance presented itself in the consideration of what foods should be included in life raft rations. In this case, spatial economy demanded that only the most necessary food stuffs be included. Experiments disclosed that without adequate calories protein balance could not be maintained, and that the nitrogen loss is minimal with mere carbohydrate. In parenteral feedings, the same situation holds true. It is useless to infuse amino acid solutions unless adequate calories can be provided for their retention. It is unfortunate that restriction of calories produces a negative nitrogen balance paralleling that of protein restriction. Nitrogen retention was maximal in depleted animals on a nonprotein basal caloric intake equivalent to 1,248 calories per square meter per day. It was estimated that the minimal activity of bed rest in humans would increase their requirement to at least 1,500 calories per square meter per day for maximum protein retention. Normal individuals on a semistarvation diet with normal activity required 2,500 to 3,000 calories a day to maintain nitrogen equilibrium on a diet which contains 60 to 70 grams of protein. Some of these calories can come from the patients' own fat stores but there is a difference in this respect between obese people and the normal lean subjects used by Keys (6) in his experiments. During the first 12 weeks of starvation, pure fat loss accounted for only 37 per cent of the gross average body weight loss. Keys (7) quotes Newman who studied 10 normal soldiers who subsisted on a 900 calorie survival ration for 9 days. There was an average nitrogen loss of 15 grams. Patients with chronic illnesses

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would be comparable to Keys semistarved normal individuals. Munroe has reviewed the interrelations between protein fat and carbohydrate in the diet. He concludes "on a fixed and adequate protein intake energy intake becomes the determining factor in N balance" and that even under normal circumstances addition of extra energy to an adequate diet usually leads to nitrogen retention. Benditt (4) found that there was no ceiling on the nitrogen retention of fed protein when adequate calories were supplied. When attempts are made to maintain nitrogen balance with intravenous feedings, it is essential that adequate calories are infused. This is especially true in infants, debilitated or chronically ill patients, and patients who may have to be maintained for prolonged periods on intravenous feeding. Also in cases of renal shutdown, a high caloric low protein intake is essential to achieve minimal protein breakdown (i.e., maximal protein sparing).

The achievement of adequate caloric intake via the intravenous route has suggested three main avenues of approach: infusions of (1) carbohydrate in the form of sugar, (2) alcohol, and (3) fat in the form of emulsions.

With the use of glucose, high concentrations are required so that the volume of injected fluid can be confined to a minimum which introduces two new problems: urinary spillage and vascular sclerosis. Urinary spillage is said to be reduced by the substitution of invert sugar for glucose. Beal has shown that invert sugar has no superiority over glucose. Its chief advantage appears to be theoretic and even that is rather tenuous. Glycogen would be ideal since the osmotic difficulties would be overcome. This carbohydrate has been used experimentally. Like dextran it is a plasma expander which may be a disadvantage. Since it is improbable that glycogen will ever be of more than theoretic interest, it is not pertinent to this present discussion. It will suffice to say that the inadequacy of intravenous sugar in meeting the caloric needs has focused attention on alcohol and fat.

That alcohol can be utilized by the body to spare protein was known to the older investigators. Atwater and Benedict pointed out that teetotalers may respond to alcohol by an excessive loss of nitrogen rather than by nitrogen retention. They believed that alcohol was a proteinic poison because it had a disintegrating tendency on body protein. The present day interpretation of their data would be that the administration of alcohol constitutes a stressful situation to abstainers, and would induce gluconeogenesis via the pituitary adrenal mechanisms. Strang and associates have frequently observed an initial protein loss and a latent period of about 1 week before protein sparing occurred. In dogs, alcohol is utilized in small doses after an initial lag but is toxic in larger quantities. One disadvantage is that it is slowly utilized and is obligatorily metabolized. It cannot enter into the normally extant energy pools. This obligatory metabolism may cause a rise in the basal metabolic rate of 28 per cent. Although alcohol can spare some protein, its value is below that of fat and at best it can be dismissed as an inadequate substitute for fat.

Starting in 1945, one finds an increasing number of studies on the use of fat emulsions intravenously to supply calories. The chief problems encountered were physical and biologic. The physical problems concerned themselves with the process of manufacture, sterilization, and assurance of stability of the manufactured product. To achieve fine emulsion particle size, the addition of moderately toxic emulsifying agents such as phospholipids were necessary. The phospholipids become toxic on aging and produce granulomatous lesions on injection. Some investigators have used protective colloids. Our work indicated that the best emulsions are formed by precipitation of fat from an acetone water solution and subsequent removal of acetone by vacuum distillation (9). A similar method has been utilized by Payne and his associates. The biologic difficulties appear to be more insurmountable. Brunschwig (5) pointed out that fat emul-

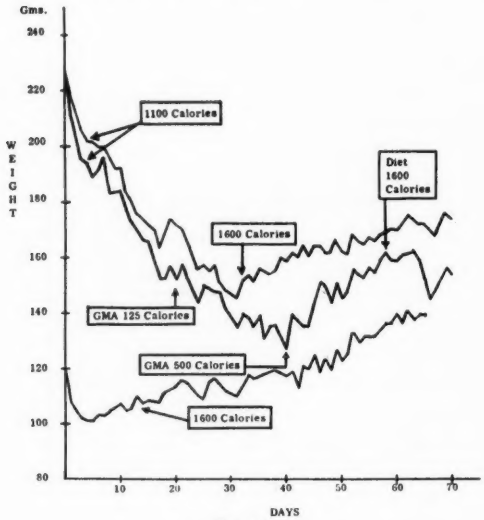

FIG. 1.

FIG. 1. At the onset of the experiment, 3 heavy rats consumed a fat free diet containing 1,100 calories per square meter per day. Two of these rats are indicated on the graph and the third on a later graph. Three light rats at the lower part of the graph consumed the 1,100 calorie diet to which 500 calories of fat (tripalmitin) were added to make a total of 1,600 calories. The weights of these rats are averaged. On the twentieth day, 1 rat on the 1,100 calorie diet was given one fourth of the theoretic fat replacement, i.e., 125 calories, in the form of subcutaneously injected GMA (indicated on the graph). The animal lost less weight but did not start to gain until the fortieth day when 500 calories of GMA were injected. The animal then gained weight at the identical rate of those animals given the 500 calories by mouth in the form of tripalmitin. On the sixtieth day, the parenterally injected GMA was discontinued and 1,600 calories given by diet. There was little change in the rate of weight gain. The other rat on the 1,100 calorie diet was given the 1,600 calorie diet 32 days after an 83 gram weight loss which represented 36 per cent of initial body weight. The animal responded with a weight gain paralleling the weight gain in the 1,600 calorie group. It is also identical to the weight gain of the animal given 1,600 calories by the injection of 500 calories of GMA.

sions which are stable in vitro may not be stable in vivo. LeVeen has shown that gamma globulins cause the emulsions to break. This could account for granulomas which have occasionally been encountered after the intravenous administration of emulsions. Infused fat emulsions are taken up by the reticuloendothelial system unlike the fat particles circulating in normal individuals after the ingestion of a fatty meal. Emulsions are often pyrogenic. The experience of some workers has been that the nitrogen losses which are induced by the pyrogenic effects of infused fat emulsions offset any favorable effect that the extra calories may have on nitrogen retention. Daily nitrogen output may increase three to fourfold in a patient with a 103 degree temperature. Lambert has shown this reaction to occur in the absence of pyrogen.

In addition, the fat emulsions are mildly hemolytic and produce anemia. Even normally occuring lipemic plasma is hemolytic. Increased red blood cell destruction occurs in dogs after fat injection. Experimentally, high fat diets will produce a hemolytic anemia. The body reduces the hemolytic activity of fats by introducing them slowly into the circulation. Fats are not absorbed from the gastrointestinal tract directly into the blood stream but appear instead in the lymph and are slowly delivered into the blood stream via the thoracic duct. Unfortunately, intravenous infusion of fats cannot circumvent this difficulty. If one could synthesize an energy rich water soluble molecule, it would be definitely superior to a fatty emulsion no matter how the emulsification is accomplished. This new molecule must be nontoxic, water soluble, nonhemolytic, enter into energy pools and not be obligatorily metabolized, and have sufficient molecular size to obviate the difficulty of a hypertonic solution. Initially, the problem might seem insurmountable and hence the solution to the problem is presented in the chronology of its disclosure.

THEORETIC CONSIDERATIONS

The first and immediate answer seemed to present itself in the water soluble spans and tweens. These substances are polyalcohol esters of fatty acids; and some are water soluble. When these substances were investigated, it was found that they were acutely toxic and produced rapid death after intravenous administration. The shock-like death was secondary to a widespread increase in

capillary permeability. In addition, these compounds were hemolytic. These substances, sorbitol, and a fatty acid, which by themselves were nontoxic, became extremely toxic when combined. The explanation was that the new molecule was surface active and its detergent properties were responsible for its toxicity. The surface activity produced hemolysis by dispersing the lipid constituent of the red cell envelope. This effect of surface active agents should have been anticipated since the bile salts have long been known to be toxic. Also, the effect of surface active agents on the potential of nerves and muscles have been shown to be similar to injury, and actual cytolysis results.

These compounds were toxic because they were surface active, but why were they surface active? Surface activity results from the configuration of the molecule. There is a fat soluble portion in the molecule and an even more strongly water soluble portion. The fat soluble portion is the long straight hydrocarbon chain (nonpolar) and the water soluble portion is the carboxy group with its polyalcohol ester (polar). Polar-nonpolar compounds of this type are surface active. The nonpolar portion of the molecule engages the lipid in the red cell membrane, and the polar portion literally pulls this lipid out into the surrounding aqueous phase. When lipemic plasma is cleared, free fatty acids are liberated from neutral fats regardless of whether the lipemia is secondary to infusion of emulsions or is of alimentary origin. This hydrolysis of neutral fats is the essential part of the clearing mechanism. The freed fatty acids are rapidly bound to plasma albumin. When the serum albumin combining capacity is exceeded, these fatty acids might exert a change on the surface of the red cell. The carboxyl group (COOH) on the fatty acid is polar while the remainder of the chain is nonpolar. This might explain why high fat diets in themselves can cause some degree of red cell hemolysis leading to a hemolytic type of anemia.

Compounds which have polar groups at both ends of the hydrocarbon chain should

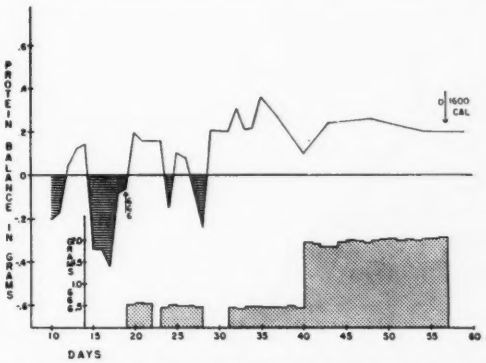

FIG. 2. The nitrogen balance on the rat receiving the full caloric replacement of GMA is shown. The administration of just 125 calories of GMA arrested a good proportion of the nitrogen loss. A substained high gain was produced with the full 500 calorie replacement with GMA.

not be hemolytic. The dicarboxylic fatty acids $(COOH)\text{-}(CH_2)_n\text{-}(COOH)$ are such compounds. Disodium sebacate is not hemolytic. Because of its short chain length, a portion of ingested sebacic acid appears in the urine. A 16 carbon dicarboxy fatty acid was metabolized to supply calories for a normal dog when given by mouth or injected. We synthesized the carbon dicarboxyl fatty acid (hexadecanedicarboxylic acid) and investigated the possibility of using this substance as a fat substitute. The material precipitated in serum as the calcium salt. On injection, embolization and hypocalcemic tetany resulted. The free acid itself is not suitable for intravenous administration. The carboxyl groups would have to be esterified if the compound was to be used intravenously. Suitable esters cannot readily be formed since polymer formation is favored. Although this blind alley was a delay, it is probably fortuitous since the dicarboxy fatty acids cannot enter the body energy pools and seem to be obligatorily metabolized. This theoretic objection may still not be of sufficient practical importance to preclude their use.

Why not make a compound with hydroxyl groups interspersed along the long nonpolar chain of a fatty acid? This procedure should render the fatty acid chain polar and the surface activity of the free fatty acid should dis-

FIG. 3.

FIG. 3. Rats represented by the upper curve of the graph were given 1,100 calories per square meter per day in the form of a fat free diet. The animals designated by the lower curve were given the identical diet, but 500 calories of purified tripalmitin were added so that the total was 1,600 calories per square meter per day. In 1 animal, an equivalent of 125 calories of GMA were injected on the twentieth day. The animal lost less weight than the animal on the 1,100 calorie diet but did not start to gain weight until the fortieth day when the amount of GMA was increased to 500 calories. The animal on the 1,100 calorie diet was given an injection of glucose equivalent to the amount of glucose contained in 500 calories of GMA which did not influence the animal's weight loss and the animal died on the fortieth day of the experiment after a weight loss of 98 grams which represented a total of 42 per cent of the initial body weight. The animal receiving GMA was able to survive on an otherwise fatal starvation diet.

appear. This conjecture proved to be correct. After synthesizing a number of hydroxyl fatty acids, one was most promising.

ALEURITIC ACID

Aleuritic acid is a naturally occurring trihydroxyl fatty acid which forms a major constituent of shellac and can be extracted from it. It has 16 carbon atoms with hydroxyl groups on the ninth, tenth, and sixteenth (terminal) carbon atoms. It is only 0.1 per cent soluble in cold water.

Rather than to prepare large quantities of this material, its metabolism by tissue homogenates (rat liver mitochondria) was tested in a Warburg apparatus. These experiments, although incomplete from a biochemical viewpoint, did indicate that the oxygen uptake and metabolism of this substance as substrate, was almost identical to its 16 carbon homologue, palmitic acid.

Since the free acid is precipitated as the calcium salt in serum, an ester of this substance was made to tie up the free carboxyl group. A monoglyceride ester increased the water solubility from 0.1 to 1.3 per cent. Finally, the synthesis of the glucose ester was achieved. This substance is completely water soluble, is stable, and can be autoclaved.

GLUCOSE MONOALEURITATE (GMA)

This ester is a colorless waxy substance which is miscible in water in all proportions. The compound has a theoretic molecular weight of 467. A 13 per cent solution of GMA is isotonic with 5 per cent glucose (molecular weight of glucose is 180). One gram of GMA requires 1.85 grams of oxygen to convert it into CO_2 and H_2O. It, therefore, has a respiratory quotient of .815 which is midway between fat and carbohydrates. It yields 6.24 calories per gram which also stands midway between fat and carbohydrate.

METABOLIC AVAILABILITY OF GMA

The evidence for the metabolic availability of glucose monoaleuritate is based upon experiments done with rats. In these experiments, injected GMA was substituted for orally fed tripalmitin. These experiments are reported in detail elsewhere, but are summarized briefly as follows.

One group of growing rats was placed on a synthetic diet containing purified fat protein and carbohydrate in definite proportions. The rats were given 1,600 calories per square meter of surface area per day of which 500 calories were from tripalmitin.

In another group, GMA was substituted for oral tripalmitin by the parenteral injection of a 10 per cent aqueous solution subcutaneously in sufficient amount theoretically to supply the missing 500 calories of fat.

In the third group, the fat was omitted from the diet so that these rats received only 1,100 calories per square meter of surface area per day.

Those rats which received only 1,100 calories per square meter per day lost weight, while those that received 1,600 calories per square meter per day gained weight (Fig. 1). Although the replacement of 125 calories in the form of injected GMA exerted a favorable influence on nitrogen balance, the rats did not gain weight until the full equivalent of 500 calories was injected. When 500 calories of GMA were injected, the gain in weight was identical to that of the rats receiving 500 calories of oral tripalmitin (1,600 cal. diet). The favorable effect on nitrogen balance provided by partial and full replacement of calories with GMA is seen in Figure 2. In other words, injected GMA can be isodynamically substituted for oral tripalmitin with identical effect on weight gain and nitrogen balance.

Those rats receiving 1,100 calories per day not only lost weight but if the diet was continued died of starvation (Fig. 3). If 10 per cent GMA was administered subcutaneously in the amount of 125 calories, the weight loss was reduced and a favorable effect was seen on nitrogen balance (Fig. 2). Additional replacement with GMA to total 1,600 calories per day caused a weight gain and a positive nitrogen balance. The possibility that the effect was not merely due to the glucose content of GMA was excluded. An amount of glucose equal to that contained in GMA was injected into an animal receiving the 1,100 calorie diet. This injection did not prevent weight loss or death (Fig. 3). The experiment demonstrated that GMA as the sole source of additional calories could sustain and induce a weight gain on an otherwise fatal starvation diet.

TOXICITY OF GMA

Incubation of human red blood cells in a 1 per cent solution of GMA buffered at 7.3 for 1 hour at 37 degrees C. induced no hemolysis. Animals receiving GMA had normal hemoglobin and red cell concentrations at the beginning and at the conclusion of the experiments.

Autopsy and microscopic sections failed to reveal any abnormality in animals receiving GMA. The site of subcutaneous administration showed no change after 2 weeks of injection. No attempt was made to determine the upper limit of tolerance but as much as 1.5 grams of the material have been given in 1 dose without evidence of toxicity.

After the subcutaneous administration of 6 grams of GMA, no more than a trace of it or of aleuritic acid could be detected in the urine.

SUMMARY AND CONCLUSION

Glucose monoaleuritate is a synthetic water soluble fat substitute. Because of the presence of hydroxyl groups on the fatty acid portion of the chain, the compound is not a polar-nonpolar type of compound and, therefore, has no detergent or surface active properties. The absence of surface activity makes the compound completely nontoxic.

Experiments have shown that parenterally injected glucose monoaleuritate is metabolically available to the experimental animal. The animal utilizes the theoretic number of calories in a manner identical with orally fed material fat.

The demonstration that a water soluble high calorie nontoxic synthetic substance can be infused to supply calories without the danger of hemolysis of red blood cells opens up new possibilities in clinical medicine. It makes possible the prolonged maintenance of adequate nutrition via the intravenous route. Without an effective calorie infusion substance, it is now impossible even with amino acid solutions and glucose adequately to maintain depleted patients in nitrogen balance. The clinical application of glucose monoaleuritate can alter our concepts of nutrition in the semistarved, thin, or depleted patient who cannot take adequate food by mouth.

REFERENCES

1. Atwater, W. O., and Benedict, F. C. An experimental inquiry regarding the nutritive value of alcohol. Proc. Nat. Acad Sc. U. S., 1902, 8: 235.
2. Beal, J. M., and Smith, J. L. The metabolism of fructose in man. Surgery, 1954, 36: 243.
3. Benditt, E. P., Humphreys, E. M., Wissler, R. W., Steffee, C. H., Frazier, L. E., and Cannon, P. R. I, The interrelationship between protein and caloric intakes and their influence upon the utilization of ingested protein for tissue synthesis by the adult protein depleted rat. J. Laborat. Clin. M., 1948, 33: 257.
4. Benditt, E. P., Woolridge, R. L., and Stepto, R. II, The relationship between the level of protein intake and the rate of protein utilization by protein-depleted men and rats. J. Laborat. Clin. M., 1948, 33: 269.
5. Dunham, L. J., and Brunschwig, A. Intravenous administration of fat for nutritional purposes; experimental study. Arch. Surg., 1944, 48: 395.
6. Keys, A., and Brozek, J. The Biology of Human Starvation. Minneapolis: The University of Minnesota Press, 1950.
7. Idem. Body fat in adult man. Physiol. Rev., 1953, 33: 245.
8. Lambert, G. F., Miller, J. P., and Frost, D. V. Febrile response following intravenous administration of fat. Am. J. Physiol., 1951, 164: 490.
9. LeVeen, H. H., Papps, G., and Restuccia, M. Problems in intravenous administration of synthetic and natural fats for nutritional purposes. Am. J. Digest. Dis., 1950, 17: 20.
10. Munroe, H. N. Carbohydrate and fat as factors in protein utilization and metabolism. Physiol. Rev., 1951, 31: 449.
11. Payne, M. A., Lazzarini, A. A., Brott, N., and Beal, J. M. Preparation of colloidal fat suspensions for intravenous use. Proc. Soc. Exp. Biol., N. Y., 1955, 89: 122.
12. Strang, J. M., McCluggage, H. B., and Evans, F. M. The nitrogen balance during dietary correction of obesity. Am. J. M. Sc., 1931, 181: 336.

THE DANGER OF SURGICAL DISSEMINATION OF PAPILLARY CARCINOMA OF THE THYROID

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OUR PRESENT KNOWLEDGE of cancer is comparable, in many ways, to the knowledge of infectious disease a century ago. At that time, the concept of infection disregarded anything that could not be seen. It is the same today in regard to cancer. Too often we give no thought to the invisible cancer cells which cling to our needles and to our hands and we spread disease as certainly as did the hands of the obstetricians in Vienna's lying-in hospitals. The surgical dissemination of papillary carcinomas of the thyroid is an example.

A papillary carcinoma of the thyroid is like a pimple: if it is left alone or treated gently, it is not apt to give much trouble. But if a papillary carcinoma is treated roughly, if it is pricked and squeezed, then, it can become a serious, even a fatal, disease. The following case is an illustration.

The patient was a 62 year old man, hospitalized for a urologic complaint. Routine examination disclosed 2 hard masses: one in the thyroid and the other in the lateral cervical region. He was told that he probably had cancer of the thyroid and an operation was advised. The patient said the mass could not be cancer because it had been there for years and had never bothered him. He refused operation. We compromised on a needle biopsy (the only biopsy, needle or open, that I have ever done on what I thought was a resectable cancer of the thyroid). The tumor was a well differentiated papillary carcinoma. It was excised and a modified radical dissection of the neck was done. A year later, the patient returned with a nodule in the skin at the site of the needle biopsy. The nodule was removed and proved to be papillary cancer of the thyroid growing in the skin (Fig. 1). There was no local recurrence in the area of the operation, just the nodule in the skin, well away from the scar, exactly at the site of the needle biopsy. Three years later, 4 years after the needle biopsy, the patient died of metastasis to lung and bone.

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This is the only case, in more than 70 primary operations that I have performed for papillary carcinoma, in which distant metastasis was seen to follow operation.

When a papillary cancer of the thyroid has been disseminated by an inadequate operation, it may be impossible, even by the most radical surgery, to control the disease. I have seen a patient whose first operation on the thyroid was done for a large multinodular goiter, in which the presence of malignancy was not suspected by the surgeon or reported by the pathologist. Several years after the operation there was a massive recurrence. The original slides were reviewed, and in a corner of one of them was a part of a tiny papillary carcinoma which had been cut across at the line of resection. This is the kind of cancer that is found in 1 of every 200 thyroids if it is looked for carefully, the kind that rarely causes trouble if left alone but which if cut into may prove fatal. An attempt was made to remove the recurrent cancer, but it was impossible to do so. The tumor grew back rapidly and caused respiratory obstruction. Distant metastasis soon developed and eventually the patient died.

Rapid spread of cancer, both by local implantation and by distant metastasis, often follows either operations that cut into or biopsy of small operable papillary cancer. In my experience with 107 cases of papillary carcinoma there were 23 patients who had had biopsies of the primary tumor or incomplete operations on the thyroid before they consulted me. In none of these was the primary tumor large or inoperable; in fact with 2 exceptions it did not seem that cancer was suspected at the time of the first operation. In 17 of these 23 patients, at the time

FIG. 1. Implant of papillary carcinoma of thyroid in skin at site of needle biopsy. Four years after biopsy the patient died with diffuse metastases to lungs and bone.

of the secondary operation, cancer was found seeded in skin and scar, or in muscle remote from the thyroid tumor (Fig. 2). In the 23 patients with incompletely removed tumors the incidence of distant metastasis was nearly 10 times as high as in the patients whose tumors had not been cut into. In 8 of the 23 patients with surgically disseminated cancer, secondary operations, regardless of how extensive, failed to eradicate the disease. Those disastrous results are in contrast to the excellent results obtained in a series of 84 consecutive cases in which there was no biopsy or incomplete operation before the primary tumor was removed, and in which over a period of from 1 to 18 years (an average follow-up of over 5 years) there have been no deaths from cancer and no distant metastasis developing after operation, and in which none of the living patients has local recurrence of cancer. In short, surgical treatment in the primary group has been 100 per cent effective as compared to effectiveness of only 61 per cent in the patients whose tumors were biopsied or cut into by operations that disregarded the danger of cutting into cancer (3).

In 1913, Tyzzer showed that simple massage of a cancer in a mouse could raise the incidence of pulmonary metastasis from 0 per cent in the control mice to 80 per cent in the massaged mice. These observations were confirmed by Knox in 1922 and Marsh in 1927. Tyzzer warned surgeons about the management of cancer, saying "The palpation of the mass in question in repeated physical examinations, the violent scrubbing often employed in preparing the field of operation, is almost identical with that which I have employed for the experimental production of metastases. It would be of advantage to the patient if each questionable tumor could be regarded as a high explosive the least manipulation of which should be absolutely avoided both prior to and during the operation."

The opposite view has been expressed by Hayes Martin, who stated that in the Head and Neck Out-Patient Clinic at Memorial Hospital "It has become our practice, therefore, to aspirate [needle biopsy] promptly all doubtful thyroid tumors before placing the patient on the deferred waiting list. By such a measure, a definite diagnosis of cancer has been made in many cases, and the patient given preference on the admission list."

In Tyzzer's concept of the explosive nature of cancer Martin's procedure of sticking a needle into an operable cancer could be likened to plunging a percussion cap into a box of dynamite to test whether it really is dynamite or just a lot of sawdust. In Martin's article, moreover, clawed clamps are shown grasping what appears to be tumor tissue. If such a technique were employed it is not unlikely that tumor cells could be squeezed into blood vessels and lymphatics just as Tyzzer, Knox, and Marsh have shown in the laboratory, and as R. B. Turnbull, Jr., has shown in clinical practice. Turnbull observed that specimens of blood

drawn from the mesenteric veins of patients with cancer of the colon contain few, if any, tumor cells when the primary tumor is not manipulated, but that after manipulation the blood is showered with tumor cells in 30 per cent of the cases. Even a digital rectal examination of a rectal cancer causes a shower of cancer cells in the inferior mesenteric vein. It is quite possible, therefore, that squeezing a thyroid cancer with clawed clamps could cause a similar spread into the veins and give rise to systemic metastasis. It seems likely that biopsy and manipulation of papillary carcinomas disseminate them, for the 38 per cent incidence of death from cancer and of inoperable recurrence in the cases reported by Martin and Frazell is nearly 3 times as high as the 13 per cent incidence in a comparable series reported from the Cleveland Clinic, and much higher than in a similar report, but less detailed, from the Mayo Clinic (9).

The high mortality in the Memorial Hospital series cannot be explained by showing that the Memorial pathologists placed some of the more malignant types of cancer in their papillary classification. In the Memorial Hospital series, only 47 per cent of all thyroid cancers are classified as papillary. In the Cleveland Clinic series, 59 per cent are so classified. Thus, if tumors of greater malignancy are included in either series, they are in the Cleveland Clinic's.

The extent of the disease in Martin's cases and the length of the follow-up can be estimated by review of Martin's and Frazell and Foote's papers. Similar data have been published for the Cleveland Clinic cases (3). The length and completeness of the follow-up is comparable in the 2 series. In each group there is a comparable number of patients who had had previous incomplete operations. In the Cleveland Clinic group, there are more cases in which the tumors had metastasized at the time they were first seen. For these reasons, it is unlikely that the better results in the Cleveland series can be attributed to exclusion of tumors of higher malignancy or to a more advanced stage of

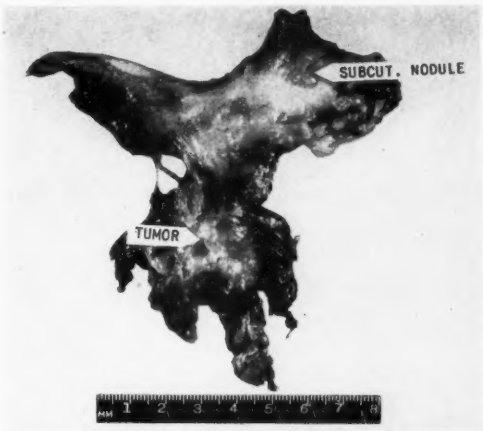
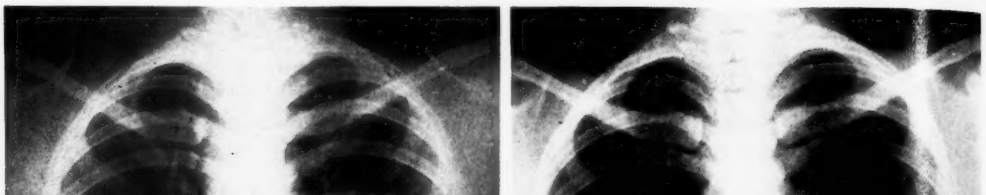


FIG. 2. Papillary carcinoma of thyroid seeded in subcutaneous tissue by an operation that cut across and disseminated cancer.

the disease at the time the patients were operated upon. It is also unlikely that the extent of the operation could have influenced the outcome, provided that it did not cut into tumor tissue. Sloan, in a large series of cases from the Presbyterian Hospital in New York, has observed that there is little correlation between the extent of the operation and the rate of cure of papillary cancers.

In addition to the dissemination of cancer by biopsy and rough manipulation of the tumor, there is another factor that influences recurrence of papillary carcinoma. This is the resistance of the host. In most cases of papillary carcinoma resistance is high, but on several occasions, when myxedema has been induced by treatment with I^{131} or by total thyroidectomy, we have observed extremely rapid growth of the metastases. It is likely that this rapid growth of the tumor is caused by thyroid-stimulating hormone of the pituitary, an excess of which is produced when there is a deficiency of circulating thyroid hormone. Conversely, when the thyroid-stimulating hormone is inhibited by giving large doses (3 grains or more daily) of desiccated thyroid, we have seen 7 cases in which metastases in lungs or bone have regressed or disappeared (2) (Fig. 3). Similar results have been reported by Balme in England.



a b

FIG. 3. a, Diffuse metastases from papillary carcinoma of the thyroid. b, Clearing of metastases after 4 years' treatment with desiccated thyroid.

Many papillary cancers of the thyroid are not autonomous but, like cancers of the prostate and breast, are to some extent under the control of the endocrine system.

Perhaps it is an excess of thyroid-stimulating hormone which causes the occasional development of clinical cancer in the microscopic foci of cancer that are present in 3 per cent of all thyroids removed at autopsy, as Mortensen, Woolner, and Bennett have shown. Perhaps it is the thyroid deficiency induced by total thyroidectomy that stimulates the production of thyroid-stimulating hormone and thus causes rapid growth and spread of some papillary cancers. Perhaps in many cases, if we gave enough thyroid to suppress the production of thyroid-stimulating hormone, it would not be necessary to remove papillary carcinomas of the thyroid. But these are conjectures. We know that excisional surgery of the primary tumor and of the grossly involved lymph nodes without removal of grossly uninvolved structures is attended by excellent long range results. Since this procedure is not deforming and rarely causes disturbances in function, it is better, for the present, to rely on surgery rather than solely on endocrine control of papillary cancers. But if surgery is to be successful, tumor tissue cannot be cut into, biopsied, or squeezed. If dissemination of the tumor is to be avoided, the operation must be performed gently and without puncturing or exposing the cancer.

In the days when tuberculosis of cervical lymph nodes was still common, the records of George Crile, Sr., show that many patients with metastases of papillary carcinomas in cervical nodes were thought to have tuberculosis of the nodes. Biopsy was not advised because of the possibility of causing a draining tuberculous sinus. These patients were treated for years, sometimes by homeopathic doses of roentgen ray, sometimes merely by diet and reassurance. Some of these patients ultimately were operated on and when the metastatic cancer in the lymph nodes was discovered it was called "lateral aberrant

thyroid tissue." Some of them had several operations for removal of nodes and since then have remained well for periods of more than 20 years despite the fact that neither the primary tumors nor all of the involved nodes were removed. In many cases of papillary carcinoma of the thyroid, the resistance of the body to the tumor is so high that fibrosis and calcification nearly, if not completely, obliterate the tumor. Many patients during the first quarter of the twentieth century must have been treated conservatively, and most of them probably lived out their lives happily unaware of the fact that they had cancer. I have followed 2 such patients, who, although untreated, have lived in good health for over 20 years with diffuse pulmonary metastases from papillary carcinomas. Both of them still are alive and well. A third patient with proved papillary carcinoma lived comfortably for 32 years without treatment and finally died of other causes.

Today, the accepted clinical management of nodules of the thyroid is quite different. Tiny nodules that in the 1920's would have been disregarded both by physician and by patient now are being cut into and biopsied, and in these cases cancer is often disseminated by the very operations that are supposed to prevent its spread. Today, we are seeing more implants of papillary cancer and more distant metastases than ever. In 1937, I was unable to find a reported case of a distant metastasis of a papillary carcinoma of the thyroid. Today, the journals are filled with reports of the dangers of papillary carcinoma, and there are many reported cases of pulmonary metastases from these tumors. Perhaps surgeons by cutting into and taking biopsies of thyroid nodules have done something positive to increase the danger of papillary carcinoma of the thyroid. Perhaps in the treatment of certain cancers, well meant attempts to cure are doing more harm than good.

SUMMARY

1. Papillary cancer of the thyroid can be disseminated and implanted both by needle biopsy and by an operation that cuts into the tumor.

2. Some papillary cancers of the thyroid can be controlled by treatment with desiccated thyroid.

REFERENCES

1. BALME, H. W. Metastatic carcinoma of thyroid successfully treated with thyroxine. Lancet, Lond., 1954, 1: 812–813.
2. CRILE, G., JR. Treatment of cancer of thyroid with desiccated thyroid. Cleveland Clin. Q., 1955, 22: 161–163.
3. CRILE, G., JR., SUHRER, J. G., JR., and HAZARD, J. B. Results of conservative operations for carcinoma of the thyroid. J. Clin. Endocr., in press.
4. FRAZELL, E. L., and FOOTE, F. W., JR. Natural history of thyroid cancer; review of 301 cases. J. Clin. Endocr., 1949, 9: 1023–1030.
5. KNOX, L. C. The relationship of massage to metastasis in malignant tumors. Ann. Surg., 1922, 75: 129–142.
6. MARSH, M. C. Tumor massage and metastases in mice. J. Cancer Res., 1927, 11: 101–107.
7. MARTIN, H. Surgery of thyroid tumors. Cancer, 1954, 7: 1063–1099.
8. MORTENSEN, J. D., BENNETT, W. A., and WOOLNER, L. B. Incidence of carcinoma in thyroid glands removed at 1,000 consecutive routine necropsies. Surgical Forum 1954; American College of Surgeons. Pp. 659–663. Philadelphia and London: W. B. Saunders Co., 1955.
9. PEMBERTON, J. DEJ. Malignant lesions of thyroid gland. Surg. Gyn. Obst., 1939, 69: 417–430.
10. SLOAN, L. W. Of the origin, characteristics and behavior of thyroid cancer. J. Clin. Endocr., 1954, 14: 1309–1335.
11. TURNBULL, R. B., JR. Personal communication.
12. TYZZER, E. E. Factors in production and growth of tumor metastases. J. Med. Res., 1913, 28: 309–332.

MEDIASTINAL LYMPH NODE IRRADIATION WITH RADIOACTIVE GOLD

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INTRAPULMONARY ADMINSTRATION of radioactive colloidal gold (Au^{198}) has recently been proposed as a possible adjunct to the therapy of bronchogenic carcinoma. The rationale for such therapy rests in part on the ability of the lymphatic system to pick up colloidal particles and carry them to the regional lymph nodes. Since the colloid is intensely radioactive, lymph node metastases could theoretically be irradiated in this manner. Because such metastases are at least partially responsible for the discouraging results of surgical resections, further investigation of this problem seemed indicated. Accordingly, a number of experiments have been carried out in this laboratory to study the effects of silver-coated colloidal Au^{198} on normal dogs employing two different methods of intrapulmonary administration. The first of these is endobronchial insufflation, and the second is submucosal injection in a lobar bronchus. The results and conclusions of these studies are presented here.

MATERIAL AND METHODS

The gold solution was supplied in an aqueous solution possessing 20 to 40 millicuries of activity per cubic centimeter. The half-life of the colloidal Au^{198} is 2.7 days and its predominant radiation is in the form of a strong beta ray (0.97 mev). which delivers over 90 per cent of the total ionization produced. The remainder is the result of a 0.4 million electron volt gamma ray. The colloidal particles of this material have been coated with a layer of metallic silver only a few molecules in thickness as originally described by Hahn and his co-worker (4, 5). These investigators have demonstrated that the silver-coated form of the colloid is more readily picked up by the pulmonary lymphatics than the uncoated suggesting greater usefulness for radiation of lymphatic metastases.

In 8 of the 25 animals studied, the radioactive material was introduced into the region of the right intermediate bronchial orifice as a spray during bronchoscopy under pentobarbital sodium anesthesia. Compressed air applied to an ordinary bronchoscopic atomizer was used. Insufflations of from 4.5 to 100 millicuries were carried out by this technique and the dogs were sacrificed at intervals of from 1 to 72 days.

After it was observed that this technique resulted in damage to the parenchyma of the lung, the submucosal route of administration suggested by Bryant and associates was employed in an additional 17 animals. A 50 centimeter 21 gauge needle with a short bevel was found most satisfactory. This was strengthened by placing it within 2 larger needles which were soldered to it. Only 1 millimeter of the inside needle was allowed to protrude from the end in order to provide

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a flange which lessens the danger of penetration of the bronchus. The proximal end of the needle was connected to fine caliber polyvinyl tubing which led to a lead-shielded syringe controlled by a calibrated screw (7). Submucosal injections of from 5 to 25 millicuries were made with this technique and the animals sacrificed at intervals of from 3 to 56 days. In order to test the technique under the most difficult conditions the right upper lobe bronchus was chosen for injection. It was believed that if satisfactory submucosal injections could be carried out in a bronchus taking off at right angles to the main stem, those more directly in line could be easily managed.

RESULTS

The dogs were studied after the stated intervals from two main points of view: the pathologic changes produced and the distribution of radioactivity.

Gross pathology. No pleural effusion was observed in the dogs subjected to endobronchial insufflation of Au^{198}, and mediastina presented no gross changes. Two dogs that had submucosal injections of the isotope displayed bilateral hydrothorax, however. In these animals, there were approximately 200 cubic centimeters of clear fluid bilaterally. In 1 dog the fluid was serosanguineous, but this was considered to represent contamination with blood at the time of postmortem examination. The mediastinal contents of 3 dogs injected submucosally showed, in addition, pronounced edema and focal areas of necrosis. The process involved only the anterior mediastinum in 1 dog (6.9 mc. dose) and the entire mediastinum in the remaining 2 dogs (20 mc. doses). The animals showing these changes were all sacrificed between 7 and 11 days after receiving the isotope. Dogs sacrificed earlier and later showed neither pleural effusion nor mediastinal edema.

The lungs of the dogs receiving endobronchial insufflation of the isotope invariably showed wedge-shaped areas of induration in the treated lobe, extending to the visceral pleura. These areas were red and hepatized with multiple necrotic foci. The lesions were sharply circumscribed and displayed a hyperemic border. In dogs sacrificed several weeks after insufflation, these consolidated areas were firm and fibrotic. Frequently there was gross evidence of radionecrosis in adjacent lobes and occasionally in the contralateral lung. The bronchi to the involved segments were patent, but the mucosa was a dirty gray-yellow color with areas of frank ulceration.

Following submucosal injection the pulmonary parenchyma presented a normal appearance. In only 2 instances was it possible to detect the site of the previous injection grossly. In these instances a hemorrhagic area in the bronchial mucosa was noted which was approximately 0.5 centimeter in diameter; histologically, it displayed central denudation of the bronchial epithelium and was surrounded by a zone of hyperemia. In the other cases, the site was localized as accurately as possible by monitoring with a Geiger counter, and sections were taken in the area with the highest count.

Nodes which subsequently proved to contain large amounts of radiation were enlarged, firm, and congested in appearance. On cut section, some of them displayed frank necrosis with liquefaction or a cheesy consistency. In dogs injected submucosally, the number of nodes found and the magnitude of the changes they displayed were roughly proportional to the size of the dose administered. The spleen, liver, kidney, and bone marrow presented no gross pathologic changes.

Microscopic pathology. Routine hematoxylin and eosin sections were used applying the method of Elftman and Elftman for the demonstration of gold particles when indicated. A definite histologic sequence of events in the lungs and lymph nodes in response to the presence of silver-coated Au^{198} can be identified for the microscopic studies. The nature of this response is much the same regardless of the method of administration of the isotope. Its severity varies according

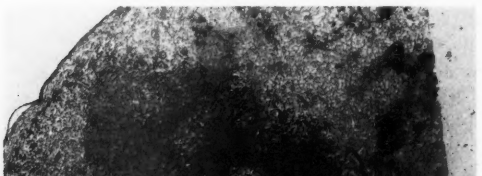

FIG. 1. Lung. Massive necrosis of pulmonary parenchyma 8 weeks after endobronchial insufflation. Only a ghost-like mosaic of structure persists; there is fibrinoid necrosis and no appreciable inflammatory reaction. Dog 7, 50 millicuries. Hematoxylin and eosin, × 9.

to the concentration of the isotope and, therefore, differs in endobronchial insufflation and submucosal injection. For purposes of discussion it seems most logical to outline first the histologic changes in relation to temporal sequence, and then to describe the difference in the severity of the process following the two modes of injection.

Histologic changes in the lungs. When the insufflation technique is used, the bronchial epithelium initially displays a ballooning of the cytoplasm with pyknosis or karyolysis of nuclei followed by sloughing of the cells. This change is noted as early as 1 day. Somewhat later, there is active regeneration of the bronchial epithelium with large cells containing eccentric nuclei bridging the surface. The individual cells vary in size, shape, and tinctorial qualities and frequently assume a bizarre appearance. This change persists up to 10 weeks.

The first change noted in the alveoli of these animals is the presence of proteinaceous material and intense congestion. Later alveolar septa show necrosis and frequently assume a fibrinoid appearance. This change is noted as early as 1 day. There is a marked proliferation of alveolar phagocytes which occasionally form a syncytial network lining the septa. Hyaline membranes are noted shortly after instillation of the isotope as well as intra-alveolar hemorrhage. There is almost inevitably an early polymorphonuclear leucocytic infiltration of the involved portions of the lung followed by a chronic inflammatory cell infiltration later. These changes are well developed at 7 days. Focal areas of necrobiosis assuming a wedge-shaped configuration with the base toward the pleural surface are noted. At a later date, only ghost-like replicas of the involved pulmonary parenchyma remain. The septa show fibrinoid necrosis, and the entire area assumes a hyaline appearance (Fig. 1).

Reparative phenomena are observed at as early as 7 days. There is fibroblastic proliferation from the alveolar septa with eventual organization of the damaged pulmonary tissue (Fig. 2). The fibroblasts often display marked atypism. Frequently, the fibrinous alveolar exudate shows early organization reminiscent of the changes encountered in uremic pneumonia. Organization of the damaged pulmonary parenchyma is almost complete at 11 weeks. These histologic changes strongly suggest that the involved segments of lung were incapable of function.

The pulmonary vasculature likewise exhibits profound changes. There is early swelling of the endothelial cells followed by fibrinoid necrosis (Fig. 1) and occasionally necrotizing arteriolitis. Thrombi are present in the larger branches of the pulmonary artery. In the later stages there is organization and recanalization of these blood vessels.

There is a distinct difference in the changes found in the pulmonary parenchyma following the two methods of administration. After endobronchial insufflation, advanced pulmonary damage is almost invariably found (Fig. 1). Not infrequently, there are radiation changes in adjacent lobes and occasionally in lobes of the contralateral lung. Following submucosal injection, however, the histologic changes are localized at the site of injection (Fig 8). The overlying epithelium displays the previously mentioned cytologic aberrations but no frank ulceration is noted. The cartilage and smooth muscle are unaltered. Beneath

the cartilage and smooth muscle there is localized necrosis and gold particles are present. The immediately adjacent lung tissue shows proteinaceous material in the alveoli, hyaline membranes, syncytial proliferation of alveolar phagocytes, and occasional fibrinoid change. These pulmonary changes are microscopic and sharply localized following submucosal injection and no lesions are found in the adjacent lobes.

Histologic changes in lymph nodes. The earliest changes in the lymph nodes consist of an agglutination of lymphocytes (Fig. 3) followed shortly by karyolysis (Fig. 4) and to a lesser degree by pyknosis and karyorrhexis. This is associated with edema and dilatation of sinusoids. Plasma cells are frequently abundant. This change is noted at as early as 1 day. Later there is dissolution of nodal architecture with loss of follicular structure. The lymphocytes display the most profound changes while the large mononuclear cells and reticulum cells appear little affected in many nodes.

At as early as 11 days some nodes present a homogeneous, hyaline appearance punctuated by large mononuclear and reticulum cells (Fig. 5). In many experiments this hyalinization is extensive and represents a striking histologic change. Not infrequently, there is a proliferation of sinusoidal histiocytes and the sinusoids are filled with

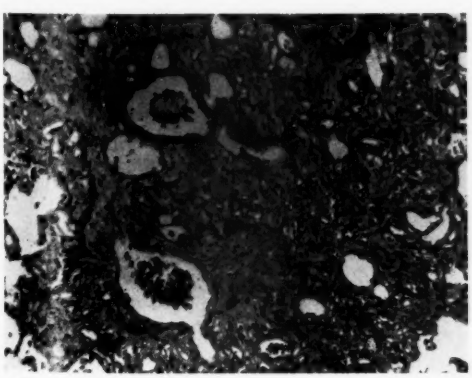

FIG. 2. Lung. Focal fibrosis with deposition of collagen 8 weeks after endobronchial insufflation. There is no appreciable inflammatory component at this time. Dog 5, 4.5 millicuries. Hematoxylin and eosin, × 67.

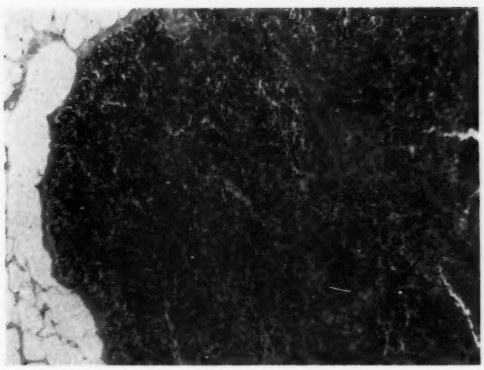

FIG. 3. Carinal lymph node. Earliest change with agglutination of lymphocytes and deposition of a smudgy basophilic intercellular matrix. Dog 6, 25 millicuries endobronchial insufflation, 1 day. Hematoxylin and eosin, × 28.

erythrocytes. Fibroplasia is noted at as early as 7 days with extension into the perinodal fat. Phagocytosis of nuclear fragments is also a prominent feature. Fibrinoid necrosis is frequently noted and is occasionally extensive. The vasculature commonly shows fibrinoid necrosis, hyaline thrombi, and occasionally necrotizing arteriolitis.

Active regeneration of the nodes is noted at as early as 1 week but is not well developed for 3 weeks. In dogs followed for 8 weeks, there is almost complete regeneration. In the most severely affected nodes, there is fibroblastic proliferation but eventual scarring does not occur. It would appear that regeneration is possible as long as reticulum cells are still present (Figs. 6 and 7).

Pathologic changes often vary both in intensity and temporal sequence. This is true not only in different nodes but also in different parts of the same node. One node might show extensive radionecrosis while another might demonstrate only focal changes. In the same node massive radiation necrosis, regeneration, or fibroplasia can coexist. It would seem that the isotope does not reach a given lymph node in one wave, but rather in succeeding waves of dispersion and that different parts of the node pick up the colloid at different times.

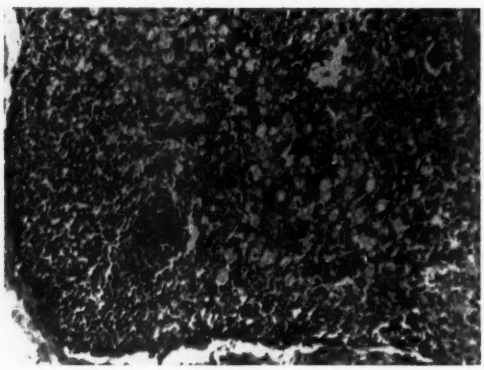

FIG. 4. Carinal lymph node. Early radiation change manifested by agglutination of lymphocytes and "ballooning" of cytoplasm. Dog 6, 25 millicuries endobronchial insufflation, 1 day. Hematoxylin and eosin, × 67.

A good correlation between histologic changes and specific activity of the tissue in counts per minute has repeatedly been demonstrated.

There is a close correlation between the site of gold instillation and the anatomic site of the most severe lymph node involvement. In general, the nodes nearest the injection site showed the most marked damage. In 2 instances following submucosal injections, however, the mediastinal lymph nodes displayed much more severe changes than the carinal or intrapulmonary nodes. In many cases, there was definite evidence of involvement of contralateral lymph nodes. Although radiation effects in the dogs were generally least marked in nodes far from the site of injection, it is of note that 1 patient who received only 2 millicuries of silver-coated Au^{198} by endobronchial insufflation showed focal radionecrosis in the lower cervical lymph nodes.

There is a distinct difference in the magnitude and number of nodes showing radionecrosis with the two methods of administration of the isotope. Following endobronchial insufflation, the changes in the lymph nodes are much less impressive. There appears to be increasing nodal damage up to a dosage of 10 to 15 millicuries, but beyond this no appreciable increment in radionecrosis is noted with increasing dosages. Following submucosal injection, on the other hand, there is progressively more nodal damage with increasing dosage. The necrosis is also more widespread when this method is employed.

The mediastina of dogs that received submucosal injections display focal necrosis of the fibrofatty tissue associated with polymorphonuclear leucocytic infiltration. The lymphatics coursing through the mediastinal tissue show ectasia, swelling of the endothelial cells, and contain particulate matter consistent with gold. There is also frequent thrombosis and organization of the mediastinal lymphatics (Fig. 9).

The liver, spleen, kidneys, and thoracic vertebral bone marrow were studied histologically in all animals. The kidneys showed the most frequent changes. There was proteinaceous material in the capsular spaces and convoluted tubules in many instances. The tubular epithelium was swollen, granular, and contained particulate matter consistent with gold. It should be emphasized that these alterations were not considered serious either in extent or degree. The spleen showed lymphoid depletion and rare areas of focal necrosis. This change is seen in many conditions and cannot be definitely attributed to the gold. The livers maintained a normal lobular configuration. The only pathologic change noted which

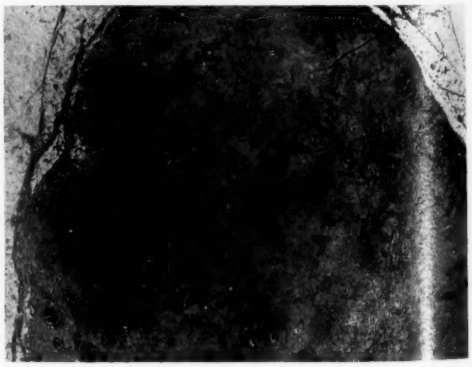

FIG. 5. Anterior mediastinal lymph node. Complete necrosis associated with hemorrhage and focal fibrinoid necrosis of blood vessels. Dog 18, 6.9 millicuries submucosal injection, 11 days. Hematoxylin and eosin, × 9.

might possibly be due to radiation was a hyaline thrombus in 1 hepatic arteriole associated with endothelial swelling and possible fibrinoid necrosis. In sections stained for gold particles, material consistent with this metal was found in the Kupffer cells in many instances. The thoracic vertebral marrow was generally not remarkable. In a few instances, focal necrosis was encountered (Fig. 10). In such cases there was serous atrophy accompanied by pyknosis and karyorrhexis of the myeloid and erythroid cells. The change was similar to that noted previously in this laboratory in sections of human vertebral marrow following intracavitary and intratumor administration of Au^{198} (1).

Distribution of radioactivity. The distribution of radioactivity was studied by gross autoradiographs and by direct counts on ashed tissue specimens. The autoradiographs were made by placing the entire block of intrathoracic structures (except the heart) on an 11 by 14 inch sheet of kodak blue streak x-ray film covered by a sheet of heavily waxed paper. The film and the specimen then were pressed together between plate glass and stored in the dark at 4degrees C. for an interval determined by the amount of activity in the individual specimen. At the conclusion of the exposure period the preparation was exposed to light

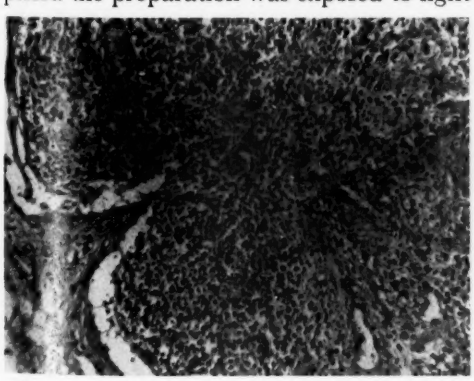

FIG. 6. Bronchial lymph node adjacent to site of successful submucosal injection of 20 millicuries. At 11 days lymphocytes are destroyed while reticulum cells and lymphoblasts persist. There is slight fibroblastic proliferation. Dog. 17. Hematoxylin and eosin, × 67.

FIG. 7. Carinal lymph node showing active regeneration of lymphoid tissue 42 days after submucosal injection. Dog 21, 6 millicuries. Reticulum stain, × 9.

for an instant prior to developing in order to outline the edges of the tissue block on the film.

Direct counts on the tissue specimens were made by placing the specimen in a weighed pyrex beaker and evaporating to complete dryness under infra-red lamps. The dry weight was recorded, and then the beaker was placed in a muffle furnace at 600 to 650 degrees C. for about 1 hour, the exact time depending chiefly on the amount of tissue to be ashed. After extracting the residue with aqua regia the washings were placed in volumetric flasks, and aliquots were pipetted out into counting planchets. The planchets were evaporated to dryness under infra-red lamps and counted under a thin mica end-window Geiger-Müller tube connected to a Tracerlab scaling circuit. Duplicate samples were made from each specimen, and each sample was counted at least twice. The results were expressed as counts per minute per gram of dry tissue weight. For uniformity in comparing data from different animals, the results were also expressed as percentages of the most active sample.

The dogs which received Au^{198} in the form of an intrapulmonary spray retained most of the radioactivity in the lobes into which it was originally sprayed (Fig. 11). However, there was definite nodal pickup in appreciable amounts. Sections from the

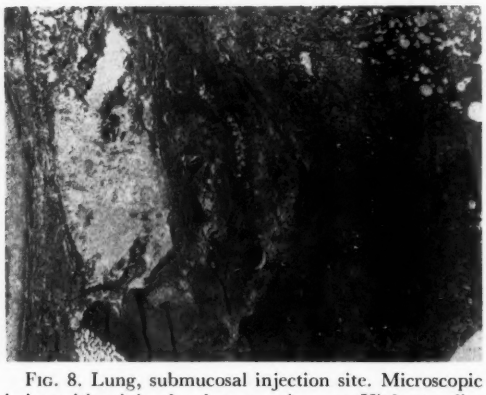

FIG. 8. Lung, submucosal injection site. Microscopic lesion with minimal pulmonary damage. Highest radioactivity in this site but 90 per cent as much found in paratracheal lymph nodes. Dog 15, 20 millicuries submucosal injection, 7 days. Hematoxylin and eosin, × 28.

liver, kidney, spleen, and bone marrow showed negligible amounts of radiation, the kidney cortex uniformly showing slightly more activity than the other organs. Although most of the radiation was confined to the lobe insufflated, other lobes often showed varying amounts of activity indicating a lack of sharp localization by this method (Table I). With the insufflation technique the lymphatic pickup was delayed, being maximal at the end of 10 to 12 days.

When the gold was administered by submucosal injection, no appreciable amount of activity was found within the pulmonary parenchyma (Fig. 12). In 5 of the dogs early in the series, the needle penetrated the bronchial wall and produced an intrapulmonary rather than a submucosal injection (Table II). These dogs had large amounts of activity within the lung, and the nodal pickup was limited; but in dogs which had true submucosal injections the bulk of the radioactivity was found in the regional lymph nodes (Table III). Not only was pickup by the lymphatics many times greater than in dogs treated with the spray technique, but the length of time required for the material to reach the nodes was also less, being marked at as early as 3 days. The pickup by liver, spleen, kidney, and bone marrow, as with the spray technique, was minimal.

The submucosal method of administration, therefore, appears to be much more satisfactory, both from the point of view of high nodal pickup and elimination of serious parenchymal damage (Fig. 13). A satisfactory submucosal injection without significant pulmonary damage was accomplished in 10 of the 15 animals in which it was attempted, most of the failures occurring early in the series. It is believed that with a very short length of the terminal needle and in the thicker human bronchus, satisfactory injections without pulmonary damage should be possible.

Following both methods of administration there was a wide variation in the amount of radioactivity found in different nodes. In general, the nodes most directly in the path of lymphatic drainage showed the most activity. Thus when the gold was administered in a diaphragmatic (lower) lobe bronchus, the carinal and bifurcation nodes usually showed the most activity; and when the material was injected around the origin of the middle (cardiac) or right upper lobe bronchi, the paratracheal nodes above the injection site showed the most activity. In 2 instances following submucosal injection, however, mediastinal lymph nodes proved to have much more activity than carinal or paratracheal nodes which were

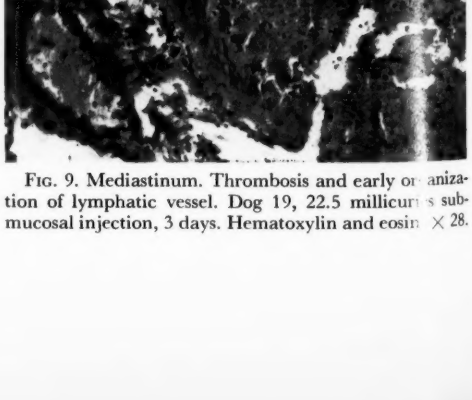

FIG. 9. Mediastinum. Thrombosis and early organization of lymphatic vessel. Dog 19, 22.5 millicuries submucosal injection, 3 days. Hematoxylin and eosin × 28.

closer to the injection site. Nodes on the contralateral side of the trachea frequently showed as much activity as nodes on the same side as the injection. Taking the data as a whole, the pattern of lymph drainage did not appear to be constant from dog to dog.

It was originally feared that administering such large amounts of radiation might produce serious illness or death. The only objective sign of any change in well-being, however, was a transient cough which developed in about half the animals in which the insufflation technique was used. This is probably due to the tracheobronchitis and pneumonitis and did not occur in the submucosal injection experiments. About 10 days following spray, 1 of these dogs exhibited a severe and persistent cough and seemed unusually sluggish. This dog had received 100 millicuries of Au^{198} by the spray technique, the largest dose administered. A leucocytosis was present during this period, and at autopsy (10 weeks after insufflation) there was evidence of organizing pneumonitis in the irradiated lobe. Presumably the cough, sluggishness, and leucocytosis were related to this process. The dog which received the second largest dose (50 mc.) showed none of these phenomena. His white count fell slowly over a period of 3 weeks to about one-half its initial level and then returned to normal. The sedimentation rate showed a transient increase shortly after injection and then returned promptly to normal. These changes are comparable to those produced by a dose roughly one-quarter this amount given intravenously (6).

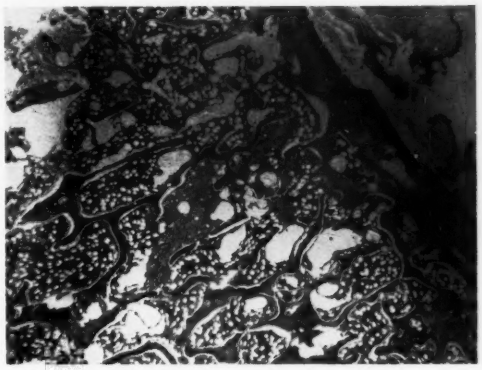

FIG. 10. Focal necrosis of vertebral bone marrow. This change was only occasionally seen. Dog 21, 6 millicuries submucosal injection with extravasation beyond bronchus. Sacrificed at 42 days. Hematoxylin and eosin, × 28.

DISCUSSION

It would appear that the most promising application of this isotope does not lie in the treatment of large tumor masses or metastases. Over 90 per cent of the radiation produced by Au^{198} is due to beta ray which has a mean penetration of 0.38 millimeter. Obviously, this beta ray can have little effect on the center of any sizeable tumor mass unless it is injected directly into the tumor rather than coated over a portion of its surface. The small percentage of gamma radiation given off is capable of penetrating large tumors; but to deliver a cancerocidal dose of gamma radiation from Au^{198} would subject the normal pulmonary parenchyma to an amount of radiation which would undoubtedly result in extensive pulmonary fibrosis. For these reasons we believe that local instillations of Au^{198} into an involved lobe could not reasonably be expected to

TABLE I.—DISTRIBUTION OF RADIOACTIVITY 3 DAYS AFTER ENDOBRONCHIAL INSUFFLATION

Specimen	*Per cent highest count*
Middle lobe (1)	100
Middle lobe (2)	50
Right lower lobe (1)	34
Right lower lobe (2)	19
Carinal node	3.3
Right cardiac lobe	1.0
Retrosternal node	1.0
Paraesophageal node	1.0
Cervical node	1.0
Left cardiac lobe	0.7
Right upper lobe	0.4
Left upper lobe	0.2
Right paratracheal node	0.2
Left lower lobe (1)	0.14
Kidney	0.11
Left lower lobe (2)	0.07
Left paratracheal node (1)	0.05
Left paratracheal node (2)	0.04
Liver	0.004
Spleen	0.003
Marrow	0.001

11.5 millicuries Au^{198} insufflated into right middle lobe orifice.

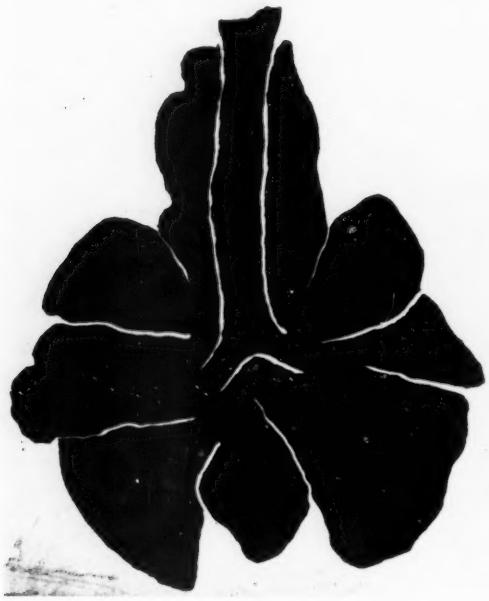

FIG. 11.

FIG. 12.

FIG. 11. Autoradiograph of lungs and paratracheal tissues. Dog 1, 11 days after 9 millicuries Au^{198} insufflated into right lower lobe. Note the large amount of radiation in the sprayed lobe and the small amount in carinal and paratracheal nodes. Table I shows the distribution of radioactivity.

FIG. 12. Autoradiograph of lungs and paratracheal tissues. Dog 15, 7 days after 20 millicuries Au^{198} injected submucosally into right middle lobe. Note the predominance of radioactivity in lymph nodes and the relative absence of radiation in the lung. (Light used to outline the tissue margins penetrated the trachea and accounts for the apparent activity in this area.) Table III shows the distribution of radioactivity.

produce any dramatic effect on the primary tumor unless administered in such high dosages as to be dangerous. Intratumor injections at the time of thoracotomy would seem to us to constitute a more promising approach to the control of large inoperable pulmonary neoplasms.

The control of large and extensive nodal metastases by Au^{198} also seems unlikely, not only because of the short penetration of the beta ray, but also because of the obstruction of lymphatic pathways that is invariably present. The most promising use for this isotope would appear to be in irradiation of small metastatic deposits in the lymph nodes before they are detectable grossly. These small, unseen metastases are undoubtedly one of the primary causes of the poor long term survival rates with "curative" resections. If the use of Au^{198} actually proves capable of destroying these hidden tumor cells, it may be possible to increase materially the percentage of 5 year survivals in this "resectable" group. The experimental data described demonstrate that it is possible to produce profound necrosis in regional lymph nodes following submucosal injections. Had these nodes contained small nests of tumor cells it seems reasonable to assume that they would have been destroyed.

The next logical step is the application of this technique to cases of bronchogenic carcinoma. The potential danger of parenchymal pulmonary damage by intrapulmonary injection does not seem great with the use of a very short terminal needle and with the protection afforded by the greater thickness of the human bronchus. Obstruction of the mediastinal lymphatics must also be considered, for marked mediastinal ede-

TABLE II.—DISTRIBUTION OF RADIOACTIVITY 3 DAYS AFTER FAULTY SUBMUCOSAL INJECTION

Specimen	*Per cent highest count**
Injection site	100*
Right upper lobe hematoma	68
Azygous node	22
Right superior interlobar bronchial node	14
Carinal node	10
Subcarinal node	0.5
Right inferior interlobar bronchial node	0.2
Paratracheal node	0.1
Paratracheal node	0.09
Liver	0
Kidney	0
Spleen	0
Bone marrow	0
Right upper lobe, parenchyma, peripheral	0

15 millicuries Au^{198} injected into orifice of right upper lobe. At postmortem intrapulmonary hematoma indicated that perforation of bronchus had occurred.
*Actual value 1284 counts per minute per milligram.

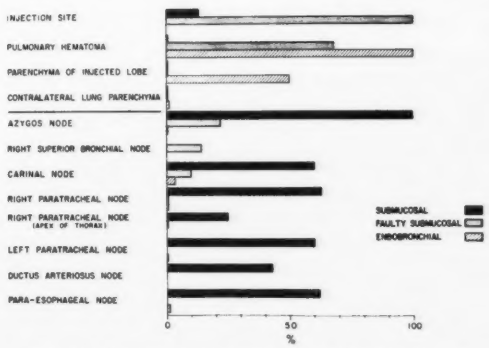

FIG. 13. Graphic comparison of distribution of radioactivity following 3 methods of administration. (Based on data contained in Tables I to III.) Note the superiority of the lymphatic permeation following true submucosal injection.

ma and moderate pleural effusion were found in dogs sacrificed from 7 to 11 days after a submucosal injection. However, in dogs sacrificed 21 to 56 days after similar injections there was no evidence of any lymphatic defect. Presumably, adequate compensatory mechanisms had developed. Finally, damage to other parenchymatous organs does not seem to be a threat for even massive doses (much larger per kilogram than would be employed in humans) failed to produce significant changes in liver, spleen, kidneys, or bone marrow. In fact, 1 animal developed a leucocytosis after receiving 100 millicuries.

In employing this technique in humans, its greatest usefulness would appear to be as a preoperative measure in early bronchogenic carcinoma. In this way, the early minute lymphatic metastases might be sterilized. After a suitable interval (a week to 10 days) a resection could be carried out. A radical lymphatic dissection should probably also be employed but it is conceivable that with proof of adequate lymph node irradiation this step might ultimately be dispensed with. Certainly the irradiation of nodes on the contralateral side of the thorax should be of great importance in improving the cure rate.

TABLE III.—DISTRIBUTION OF RADIOACTIVITY 4 DAYS AFTER SUCCESSFUL SUBMUCOSAL INJECTION

Specimen	*Per cent highest count*
Azygous node	100*
Right paratracheal node	63
Paraesophageal node	62
Left paratracheal node—midthoracic	60
Carinal node	60
Ductus arteriosus node (opposite side)	43
Right paratracheal node at apex of pleural space	25
Injection site in bronchus	13
Left paratracheal node at apex of pleural space	1.2
Right upper lobe, parenchyma	0
Liver	0
Spleen	0
Kidney	0

17.4 millicuries Au^{198} injected submucosally into orifice of right upper lobe bronchus. No hematoma in lung at postmortem.
*Actual value 655 counts per minute per milligram.

SUMMARY

1. The distribution of radioactivity and the pathologic changes produced by silver-coated colloidal Au^{198} sprayed directly into the lung or injected submucosally in a lobar bronchus have been studied in 23 normal dogs.

2. Good localization of radiation and extensive necrosis in the regional lymph nodes resulted regularly from the submucosal method of injection. Solutions sprayed into the lung tended to remain localized at the site of insufflation and were much less effective in reaching the lymph nodes. Neither method resulted in any significant systemic irradiation.

3. Clinical trial of submucosal injections of this material prior to lobectomy or pneu-

monectomy seems indicated in selected patients with bronchiogenic carcinoma to control microscopic lymphatic metastases.

REFERENCES

1. Botsford, T. W., Wheeler, H. B., Newton, R. A., and Jacques, W. E. Hypoplasia of the bone marrow associated with radioactive colloidal gold therapy. J. Am. M. Ass., 1953, 151: 788–791.
2. Bryant, J. R., Berg, H. F., and Christopherson, W. M. Localization of radioactivity in the lung and in the lymph nodes. J. Thorac. Surg., 1953, 26: 221–232.
3. Elftman, H., and Elftman, A. G. Histological methods for the demonstration of gold in tissues. Stain Techn., 1945, 20: 59–62.
4. Hahn, P. F., and Carothers, E. L. Radioactive metallic gold colloids coated with silver and their distribution in the lung and its lymphatics following intra-pulmonary administration: therapeutic implications in primary lung and bronchiogenic tumors. Brit. J. Cancer, 1951, 4: 400–404.
5. Idem. Lymphatic drainage following intrabronchial instillation of silver-coated radioactive gold colloids in therapeutic quantities. J. Thorac. Surg., 1953, 25: 265–279.
6. Wheeler, H. B., Jackson, M. A., and Hahn, P. F. Hematology of the dog following intravenous administration of radioactive colloidal gold. Am. J. Physiol. 1951, 166: 323–327.
7. Wheeler, H. B., Rubenstein, J. H., Coleman, M. D., and Botsford, T. W. Techniques and radiation precautions for intratumor injections with radioactive colloidal gold. Arch. Surg., 1952, 65: 283–289.

THE MANAGEMENT OF CRYPTORCHISM

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THE MANAGEMENT of the undescended testis has been a debatable issue among the members of the medical profession for many years. Two divergent schools of thought have emerged and at times appear irreconcilable. One view, first presented by Hunter in 1839, is that the testis fails to descend because of an inherent defect. The other opinion, which received added support by the relatively recent researches of Moore, is that the undescended testis is potentially normal, suffering only from an inimical environment. The introduction of new techniques in diagnosis and treatment have served merely to highlight the controversy. The initial successes reported with the use of gonadotrophins gave encouragement to the advocates of the "environment theory." On the other hand, the histologic data obtained by means of testicular-biopsy emphasized the unsatisfactory functional results obtained by treatment, focusing attention on the "imperfect testis" theory. It is our intention in this résumé to report on the histologic patterns of the normal and of the undescended preadolescent testis, to describe the morphologic changes that accompany descent of such testes, and to discuss the relative merits of the various methods employed in effecting descent.

INCIDENCE

Cryptorchism occurs often enough to merit the attention of pediatricians, endocrinologists, and surgeons. The incidence reaches 10 per cent in the newborn, 2 per cent in pubertal boys, and 0.2 per cent in adults. The reduced incidence from birth through adolescence is only in small part the result of treatment. Most of it reflects the high frequency of spontaneous descent. Testes that descend during the first few months of life probably have a normal potential for development, but there is a growing suspicion that those which do not descend spontaneously until the preadolescent period are either inherently imperfect or have been irreparably altered by their nonscrotal position. No statistics are available, but it would be interesting to determine how many infertile men owe their semen deficiency to delayed testicular descent even though it occurred before puberty.

SPONTANEOUS DESCENT

The mechanism of testicular descent into the scrotum is poorly understood. The role of the gubernaculum, once considered important, is no longer stressed. Instances of normal descent in the absence of a gubernaculum are not uncommon, and it is now generally agreed that the gubernaculum acts merely as a guide for the testis. The role of the processus vaginalis, which precedes the testis in its descent, is also undetermined. One gains the impression that a normal testis possesses an inherent ability to reach its ultimate destination and that it will do so unless it encounters anatomic anomalies.

FAILURE TO DESCEND

The causes of nondescent are equally obscure. Admittedly, mechanical factors, such as malformation of the inguinal canal and abnormality of either the fascial layers or the cremaster muscle, may at times be

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FIG. 1. Resting phase. Age 1 year. Tubular diameter about 65 microns. Tubules filled with undifferentiated cells. Early lumen formation. No Leydig cells.

FIG. 2. Growth phase. Age 7 years. Tubular diameter about 70 microns. Spermatogonia now easily identified. Increase of intertubular tissue. No Leydig cells.

responsible. When the testis has been halted in its descent through the inguinal canal adhesions are often found at surgery, but they are more likely to be the result of the abnormal position rather than its cause. The vas deferens rarely interferes with descent, being usually long enough; in fact it is often prolapsed distal to the testis.

The most common deterrent to descent found at operation is a short internal spermatic artery which not only prevents further testicular descent but also poses the major problem in an operative attempt to place the testis in the scrotum. The responsibility could then be put on the internal spermatic vessels if it were not for the generally accepted biologic axiom that an organ develops as adequate a blood supply as it requires. In other words, the spermatic vessels are not long enough because the poorly developing testis makes no demands for greater length. This returns us to the conclusion originally reached by Hunter, namely that in many instances the undescended testis is congenitally deficient and that its failure to descend is the result rather than the cause of the testicular hypoplasia.

Cryptorchism is encountered in a variety of endocrinopathies. In such instances, testicular nondescent is merely part of the symptom complex, unrelated to any mechanical defect. The testis is hypoplastic and, unless the primary condition is remedied, it will not develop properly even if its position is corrected surgically. Such dysplasia is well known and has been described.

Our concepts of the histologic appearance and functional capacity of the undescended testis have changed considerably since the introduction of testicular biopsy. Before this procedure came into use only extirpated testes were available for histologic study. Employing biopsy, the testis can now be studied at orchiopexy, after spontaneous or

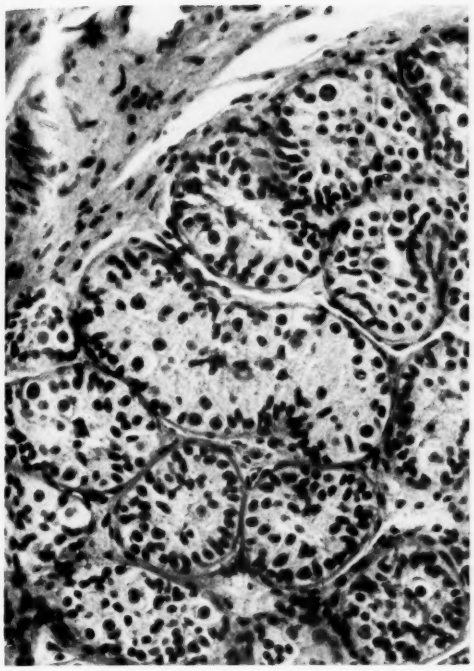

FIG. 3. Maturation phase. Age 10 years. Tubular diameter 72 to 80 microns. Tortuosity prominent. Mitotic figures in cells which are now arranged in layers. Leydig cells present.

FIG. 4. Adolescent testis. Age 14 years. Tubular diameter 130 microns. All generations of cells present including spermatogonia, primary and secondary spermatocytes, and spermatids. Leydig cells abundant.

posttherapeutic descent and serially thereafter.

METHOD OF PRESENT INVESTIGATION

All of our studies were done through the medium of testicular biopsy. The histologic appearance of the testis was observed in the following categories: (1) the normal picture from birth through adolescence; (2) after spontaneous postnatal descent; (3) after descent resulting from hormone administration; (4) during orchiopexy and at varying periods following operation; (5) infertile adults with a history of preadolescent orchiopexy.

RESULTS

The observations reported herein are based on the histologic examination of nearly 100 normal testes in patients of various ages from birth through adolescence and of 142 testes whose descent into the scrotum was effected by any one of the several methods previously mentioned.

Normal testis. Three stages of development have been described by us (1): (1) resting phase from birth to the age of 4 years; (2) growth phase from the age of 4 to 10; (3) developmental or maturation phase from the age of 10 through adolescence.

In the resting phase the seminiferous tubules are at first compactly filled with undifferentiated cells, presumably the forerunners of spermatogonia and Sertoli cells. Lumen formation, with arrangement of the cells in a single layer, occurs during this period (Fig. 1). During the growth phase, the tubule enlarges somewhat and some of the cells take on the typical appearance of spermatogonia but the number of cells remains unchanged (Fig. 2). In the maturation phase, cell division is noted, mitotic

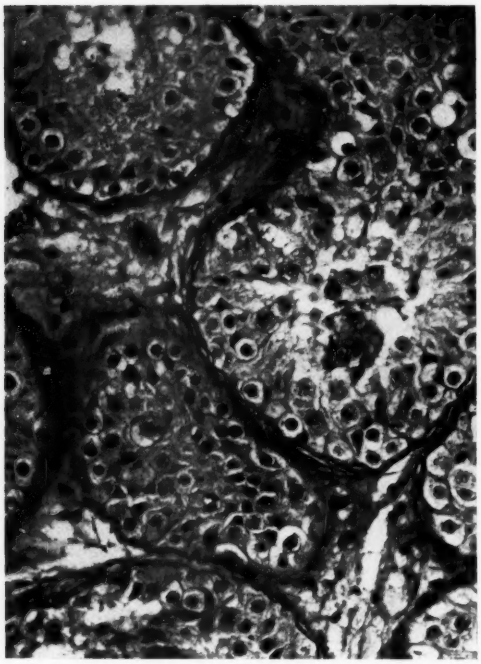

FIG. 5. Boy aged 14 years, 2 years after spontaneous descent. Tubules normal in size but cellular maturation is retarded. Many spermatogonia and a few primary spermatocytes present. Leydig cells normal.

FIG. 6. Adult aged 22 years. Spontaneous descent occurred at the age of 14 years. Tubules smaller than normal and quite sclerotic. Sertoli cells only. Leydig cells normal.

figures are numerous, and recognizable spermatocytes and spermatids appear (Fig. 3).

The age of onset of complete spermatogenesis varies considerably but takes place between the ages of 12 and 18 years (Fig. 4). The Leydig cells, present at birth because of chorionic gonadotrophin, disappear after the first week of life and do not reappear until age 10 years when endogenous pituitary gonadotrophin secretion begins.

The spontaneously descended testis. The number of such testes which have been studied is quite small and our conclusions are necessarily guarded. In 2 adolescents whose testes descended spontaneously at 4 and 6 years respectively, the histologic picture appeared normal. In a third boy in whom descent occurred at 12 years, biopsy at 14 disclosed marked retardation of development (Fig. 5). Further biopsies were refused but semen examination at the age of 17 years revealed marked deficiency in the sperm population.

The fourth patient was first seen at the age of 22 years because of infertility. He gave a history of having had a normally descended right testis at birth and a left testis which descended spontaneously at 14. Physical examination disclosed a small left testis. Testicular biopsy revealed moderately impaired spermatogenesis on the right side and marked depression of spermatogenesis on the left (Fig. 6). We concluded that both testes were hypoplastic, the left being depressed to such an extent that it lacked the capacity to descend.

Testes in which descent was induced by gonadotrophin administration. This group is divided into two categories: (1) those in which descent was effected with small doses of

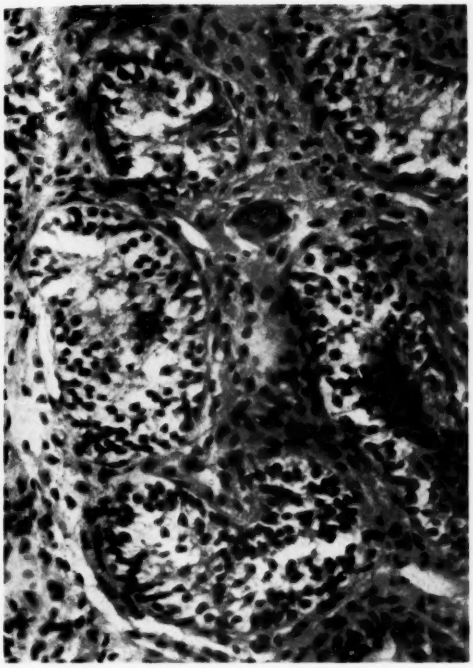

FIG. 7. Adolescent boy aged 14 years. Testis descended 1 year earlier after 10,000 international units chorionic gonadotrophin. Tubules smaller than normal displaying less advanced cellular maturation. Increased amount of intertubular connective tissue. Leydig cells normal.

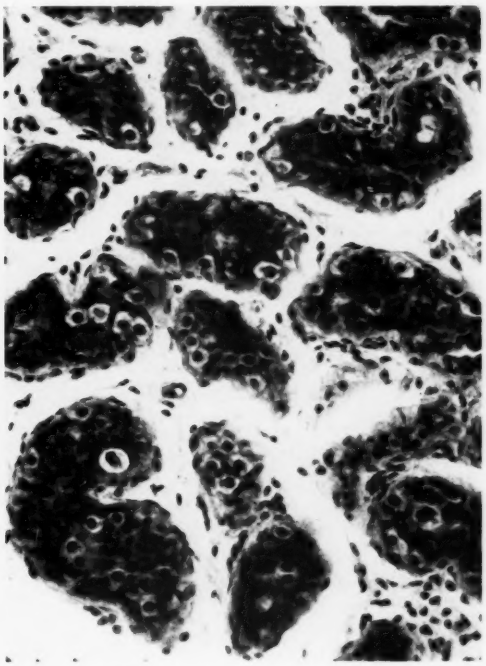

FIG. 8. Male age 19 years. Testis descended after 40,000 international units chorionic gonadotrophin. Biopsy soon after descent. Tubular size that of about age of 9 to 10. Spermatogonia prominent but no other cells can be distinguished. Leydig cells normal.

gonadotrophins, less than 10,000 international units; and (2) those which did not descend until an average of 40,000 international units had been given.

Observations in the first category are based on 14 testes biopsied following their descent as a result of small doses of gonadotrophins. These children, who were treated successfully before the age of 10 years and biopsied soon after descent, had for the most part a normal histologic picture. Those treated between the ages of 10 and completion of adolescence disclosed a variable picture, one which was quite comparable to that of the testes which descended spontaneously at similar ages (Fig. 7).

The second category consists of 8 testes which descended only after approximately 40,000 international units of gonadotrophins had been given. Biopsy of such organs showed a uniformly poor histologic picture. Five of the 8 testes had small tubules filled with poorly differentiating epithelium (Fig. 8). The remaining 3 testes disclosed marked dysgenesis, most of the tubules being small and sclerotic, only a few progressing to partial maturation (Fig. 9).

Testes subjected to orchiopexy. Bilateral biopsies were done uniformly during orchiopexy and repeated whenever permission was obtained, within a year or two following the operation.

During orchiopexy. Testes subjected to surgery in children under 10 years old disclosed histologic pictures which compared quite favorably with the normal. The opportunity for such comparison was afforded especially in instances of unilateral cryptorchism in which the nonscrotal testis was compared with its normally descended mate. Testes

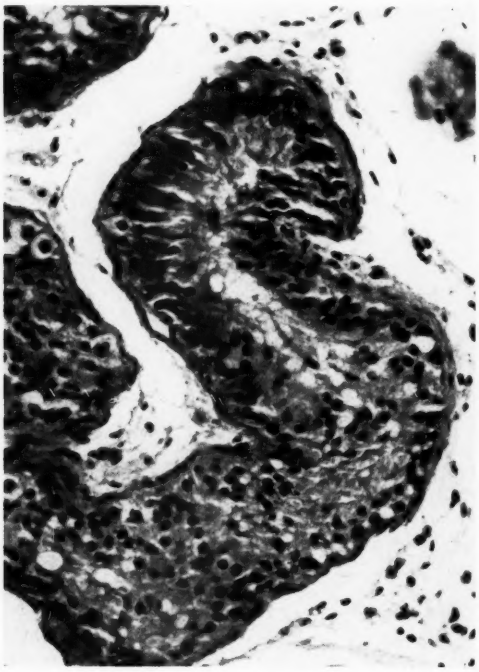

FIG. 9. Adolescent aged 17 years. Descent after 40,000 international units chorionic gonadotrophin. Biopsy 2 weeks after descent. Testis slightly smaller than normal. Tubules normal in size. Cellular development arrested at spermatocyte stage. Marked peritubular fibrosis (seen in other sections). Leydig cells normal.

subjected to orchiopexy after the age of 10 years showed varying degrees of tubular damage which were almost directly proportional to the increasing age of the child. The tubules were generally smaller and showed less advanced cellular development than the normal (Fig. 10).

Following orchiopexy. Biopsies were performed in 14 patients from 6 to 24 months after operation. Orchiopexy had been performed by a modified Torek technique. Retroperitoneal rather than cremaster dissection was employed in order to obtain greater cord length. All of these patients had good cosmetic results but the histologic follow-up disclosed considerable tubular alteration. The damage was observed even in those boys who were subjected to operation before the age of 10 years. In the testes brought down surgically after 10, subsequent biopsy showed even greater tubular damage and more advanced degenerative changes (Fig. 11).

Infertile adults with a history of orchiopexy. Of the 73 testes which had been surgically brought down, 26 were so small that it was obvious that spermatogenesis was absent. In each of these, biopsy demonstrated either complete fibrosis with destruction of even the Leydig cells or small acellular tubules with normal Leydig cells (Fig. 12). Of the remaining 47 testes, 12 disclosed tubules devoid of all cellular elements except Sertoli cells (Fig. 13), 16 showed serious spermatogenic defects consisting of a reduction in tubular size and cellular contents (Fig. 14), and only 19 contained tubules with germinal epithelium in various stages of development (Fig. 15). However, in less than 5 per cent of the tubules of even the best preserved testis did spermatogenesis proceed at a normal rate, and not a single testis could be described as the producer of spermatozoa sufficient to result in fertility.

DISCUSSION

In considering the management of cryptorchism it is necessary to have a clear picture of the reasons for treating the anomaly. These are: (1) to repair an associated clinical hernia and relieve the discomfort which these patients may experience; (2) to prevent malignant degeneration of the testis; (3) to prevent or overcome associated psychic disturbances; (4) to insure normal development of the seminiferous tubules and ultimate fertility.

No one will dispute the need for operation of the undescended testis if associated with a clinical hernia, not merely a patent processus vaginalis. With regard to malignant degeneration, it is almost universally acknowledged that orchiopexy does not decrease its incidence. To bring into the scrotum a testis which supposedly has a high incidence of malignancy in order to render it more accessible for observation is not, to our mind, good prophylaxis. If the danger

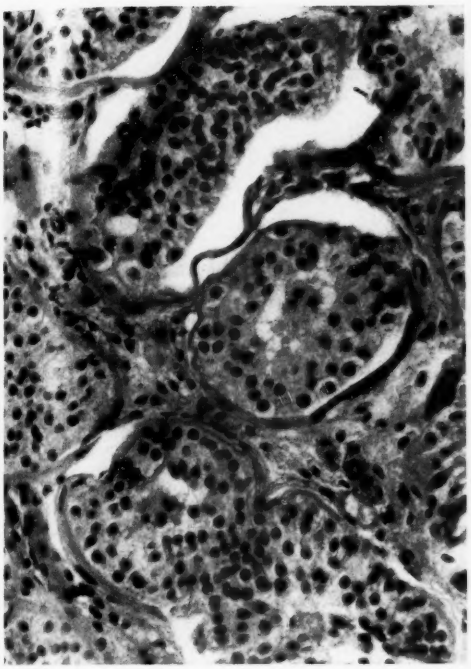

FIG. 10. Preadolescent boy aged 14 years. Appearance of testis at orchiopexy. Tubules slightly smaller and less cellular than those of normally descended mate. Cellular maturation appears only slightly retarded. Leydig cells normal.

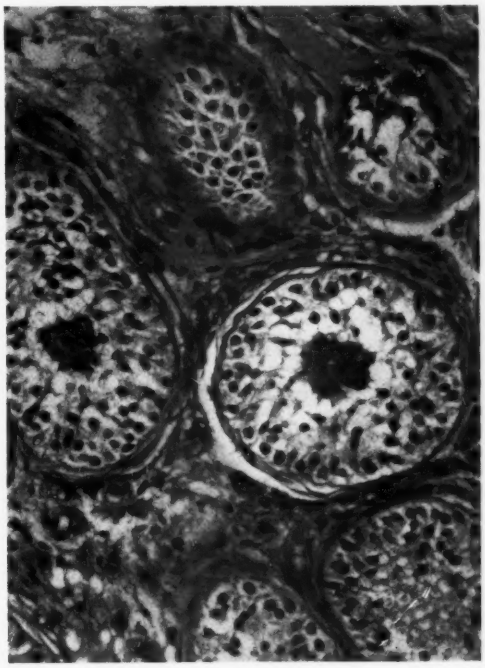

FIG. 11. Same patient as that of Figure 10, 4½ months after orchiopexy. No appreciable increase in tubular size or cellularity. Some sclerosis. Has lagged behind its normally descended mate which is now showing advanced spermatogenesis.

is carcinoma, the only sound method of prevention is orchiectomy. The problem of psychic disturbances resulting from persistent cryptorchism is one which we cannot discuss with any technical knowledge since our own experience is necessarily limited. We have observed very little disturbance in children or in adults. The literature contains very little regarding the alleged psychic trauma imposed by this physical inferiority.

The stimulation and preservation of spermatogenesis remains the most important indication for the treatment of cryptorchism. However, most observers now agree that the present methods of obtaining testicular descent have little or no beneficial effect on spermatogenesis. The recent report of Gross, revealing fertility in 80 per cent of the bilateral cryptorchids subjected to orchiopexy, stands out as a shining exception.

If one assumes that the testis which ultimately descends spontaneously is basically healthy, only temporarily retained in its nonscrotal position (generally distal to the inguinal canal), then he may reasonably conclude that such a testis retains a normal capacity for development and that it will utilize that capacity as soon as it descends into the scrotum. Even if it is accepted that the administration of gonadotrophins results in descent only of those testes that would ultimately descend spontaneously, it is imperative that the gonadotrophins be administered before the age of 10 years in order to encourage descent before the seminiferous epithelium normally begins to mature.

The results following hormone administration, however, leave much to be desired. If the wandering testis is excluded from the discussion, a large percentage of good results

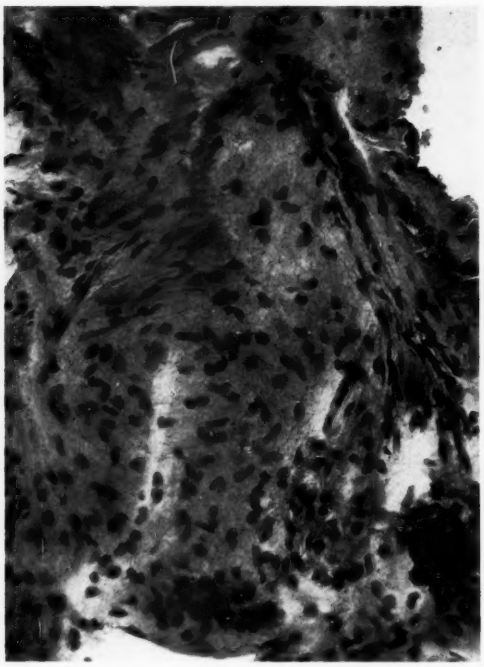

FIG. 12. Patient aged 30 years. Testis size of lima bean. Bilateral orchiopexy resulting in postoperative atrophy. Complete fibrosis following destruction of all recognizable testis tissue. Eunuchism resulting from orchiopexy.

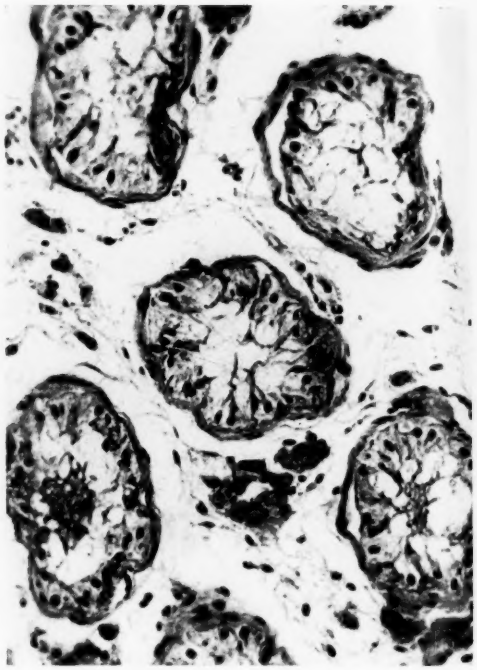

FIG. 13. Patient aged 24 years. Orchiopexy had been performed at the age of 12 years. Testis small and firm. Tubules small. Contain Sertoli cells only. Leydig cells normal.

which supposedly follow gonadotrophin administration are eliminated. Such testes require no treatment and, fortunately, receive little because descent occurs early. Perloff and Ehrlich have shown that testes which descend only after the administration of large doses of gonadrotrophins are almost uniformly aspermatogenetic. The histologic picture is similar to that following unsuccessful orchiopexy. Even when only moderate doses of gonadotrophins are required to effect descent, the resultant histologic picture as revealed by biopsy often discloses arrested spermatogenesis and fibrosis.

If gonadrotrophins are employed they should be administered before the age of 10 years. Before this age, the undescended testis shows only minimal deleterious effect from its abnormal position. After 10 years of age endogenous pituitary gonadotrophins produce stimulation of a testis lacking the capacity to respond normally. The result is retarded development with secondary degenerative changes. The administration of chorionic gonadotrophin produces a similar stimulation and the undescended testis which fails to descend after gonadotrophin administration suffers from the same lack of developmental capacity and undergoes secondary degeneration. The unsuccessful administration of large doses of chorionic gonadotrophins merely accelerates the degenerative process produced more slowly by the endogenous pituitary gonadotrophins.

The results of orchiopexy are admittedly disappointing. They were formerly judged on criteria which are today considered totally unacceptable. These were the size of the testis and its position in the scrotum. Inasmuch as semen examination is applicable only in instances of bilateral cryptorchism, comprising only about 20 per cent of the

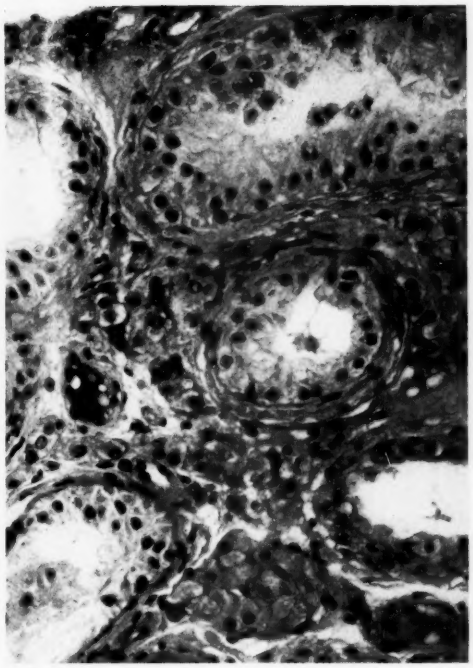

FIG. 14. Patient aged 27 years. Orchiopexy at age of 4. Tubules smaller than normal containing only spermatogonia. Peritubular fibrosis and marked hyperplasia of Leydig cells.

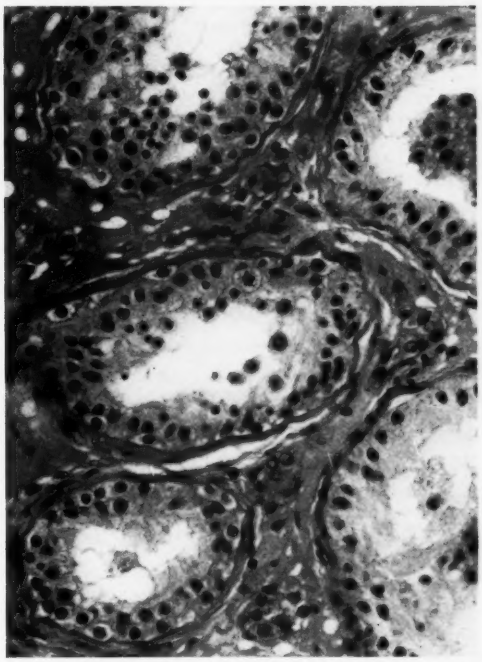

FIG. 15. Patient aged 25 years. Orchiopexy at 8. Testis normal size, in lower scrotum. Occasional tubule shows advanced cellular division. Most show arrest early. Some peritubular fibrosis and Leydig cell hyperplasia.

total number, it too is not an adequate method of evaluating the merits of all phases of treatment. Follow-up by testicular biopsy of a large series of cases discloses the fact that satisfactory spermatogenesis is found only in the exceptional case postoperatively. In a few rare instances, the testis operated upon produces a minimal number of spermatozoa, not sufficient, however, to influence fertility. In the large majority of cases (85 per cent of satisfactory cosmetic results), the testis produces no spermatozoa. In these, histologic examination discloses tubules either devoid of seminiferous epithelium or containing a reduced number of immature cells. In at least 10 per cent of the cases in which operation has been performed, the testis is completely atrophic because of interference with its blood supply during the course of orchiopexy. Such atrophy results in loss of Leydig cell function which had up to the time of operation been well preserved. In an equal number of patients, orchiectomy is wittingly substituted for orchiopexy because the anatomic structures are found inadequate for satisfactory transference of the testis into the scrotum.

A few scattered observers have developed surgical techniques which, they claim, preserve all of the functions of the testis. Gross's report of fertility in 80 per cent of bilateral cryptorchids subjected to operation before the age of 11 years is inconclusive because the number of patients which he was able to follow is small. Moreover, a considerable percentage of his good results is based on a history of subsequent alleged fatherhood, not on semen examination or testicular biopsy. Inasmuch as resort to artificial donor insemination is becoming an increasingly acceptable practice among women whose husbands are sterile, the birth of a baby to

such parents is not proof of the husband's fertility.

In summary, from the viewpoint of spermatogenesis, operation for cryptorchism, as presently performed, results in only an occasional reportable success. In nearly 80 per cent, the operation is a failure in that spermatogenesis is not improved by the procedure and, in an additional 20 per cent, operation results in planned or unintentional loss of all testicular tissue.

Orchiectomy for relief of cryptorchism and prevention of malignancy has been in practice for many years. It fell into disuse when the improved methods of orchiopexy were introduced, but it is still the method of choice in the hands of those who believe that it is a justifiable procedure in order to overcome the increased incidence of malignancy in the undescended testis. As mentioned before, orchiectomy is occasionally done if it is found impossible to bring the testis into the scrotum during orchiopexy, and finally, functional orchiectomy often results from an interference with the blood supply to the testis during the course of orchiopexy.

This leads us to the final alternative in the management of testicular nondescent—watchful waiting. We believe that it is most certainly justified in asymptomatic, uncomplicated unilateral cryptorchism. Inasmuch as unilateral cryptorchids are generally fertile, the urgency for treatment in such patients is considerably reduced. Gonadotrophins, administered in moderate doses, may be tried but are not likely to be effective. The advisability of surgery in such instances is still debatable.

However, in instances of bilateral cryptorchism the problem is quite different. The prospect of almost certain sterility is sufficient to make one feel that *laissez-faire* is not here applicable. Hormone administration followed by orchiopexy if necessary is most certainly indicated. Even if the percentage of good results is pitifully small, the salvage of a small number of men destined to be sterile, is sufficient justification for subjecting all bilateral cryptorchids to operation.

CONCLUSIONS

1. Therapeutic measures aimed at correcting cryptorchism should be instituted before the age of 10 years.

2. Testes which descend following the administration of moderate doses of gonadotrophins before 10 years of age generally display satisfactory spermatogenesis. Those that descend only after large doses of gonadotrophins possess serious spermatogenic defects.

3. The incidence of infertility in men with unilateral cryptorchism is no greater than that of the average male population. The advisability of surgical interference in boys with asymptomatic uncomplicated unilateral cryptorchism is questioned.

4. Boys with bilateral cryptorchism will become sterile men. Accepted therapeutic measures aimed at correcting such bilateral nondescent are definitely indicated.

REFERENCES

1. Charny, C. W., Constant, A. S., and Meranze, D. R. Development of the testis; a histologic study from birth to maturity with some notes on abnormal variations. Fert. Steril., 1952, 3: 461.
2. Gross, R. E. Cryptorchidism. Read before the Section on Surgery of the American Medical Association, June 8, 1955. Personal communication also.
3. Hunter, J. A description of the situation of testis in fetus with its descent into scrotum. Med. Classics, 1940, 4: 421.
4. Moore, C. R. The behavior of the germinal epithelium in testis grafts and in experimental cryptorchid testes (both rat and guinea pig). Science, 1924, 59: 41.
5. Perloff, W. H., and Ehrlich, E. B. Personal communications.

ANATOMIC AND TECHNICAL CONSIDERATIONS IN THE TREATMENT OF ESOPHAGEAL HIATAL HERNIA

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IN THE TREATMENT of esophageal hiatal hernia opinion differs relative to both the mode of surgical approach and the technique of surgical repair.

The following description of the anatomy of the esophageal hiatal ring is formulated on observations made in a dissection study of 15 fresh cadaver specimens. The anatomic findings in each dissection were recorded in detail by either of two medical art illustrators, composites of which are depicted in Figures 1 and 2.

The crura of the diaphragm arise from the anterolateral surfaces of the upper lumbar vertebrae and the intervening fibrocartilages. Characteristically, the right crus, longer, thicker, and more tendinous than the left, arises from the upper 3 and the left crus from the upper 2 lumbar vertebrae. As the right crus ascends, it separates into superficial and deep muscle layers to form completely the esophageal hiatus (Figs. 1 and 2). The thin superficial layer forms the right margin and the thick deep muscle layer forms the left margin of the hiatal ring. Anteriorly, the margin of the ring is in close proximity to both the tendinous portion of the diaphragm and the inferior phrenic vein (Fig. 1). Posteriorly, the hiatus is partially occluded by a thin veil of decussating muscle fibers and fibroareolar tissue (Figs. 1 and 2). In no instance did the left crus of the diaphragm participate in the formation of the esophageal hiatal ring. Decussation of the fibers of the right and left crura, routinely depicted in anatomic illustrations of the esophageal hiatus, was not observed.

When viewed from above the diaphragm and obliquely downward from the head of the cadaver specimen (Fig. 2), the thick deep muscle layer of the right crus, the left margin of the hiatal sling, is superficial to and crosses the superficial muscle layer of the right crus, the right margin of the hiatal sling. When projected into the right lateral prone position, the left or thick margin of the sling is anterior, the right or thin margin is posterior, and the crossing of the fibers is lateral. This relationship is depicted in the artist's illustrations (Figs. 3, 4, and 5) of the technique employed in the transthoracic repair of a sliding hernia of the esophageal hiatus.

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TECHNIQUE OF OPERATION

The technique illustrated, based on the anatomic findings previously described, was used in a consecutive series of 8 patients. In a follow-up period extending from 4 to 18 months, the results obtained were completely satisfactory.

In general, for the repair of an esophageal hiatal hernia the transthoracic route is preferred. The patient is placed in the direct right lateral prone position and the left pleural cavity is entered through the eighth interspace (Fig. 3A-E). Resection of a rib is not required. The phrenic nerve is not crushed by clamping, but temporary paralysis of the diaphragm is obtained by injection of the nerve with 6 to 8 cubic centimeters of procaine (1 per cent) solution (Fig. 3E). The deflated left lung is displaced upward and maintained in position by retraction on a moist gauze pad. This maneuver exposes the esophageal triangle, the site of the hernial protrusion (Fig. 3F).

An inverted T-shaped incision is made in the posterior mediastinal and diaphragmatic pleura, and the resulting pleural flaps

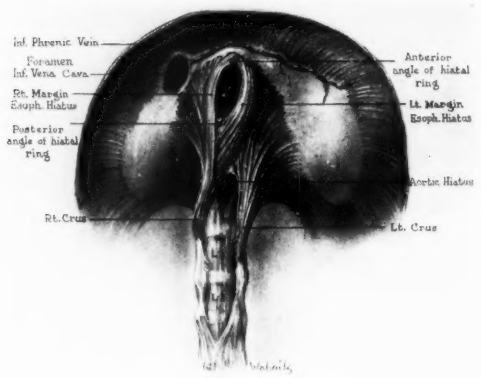


FIG. 1.

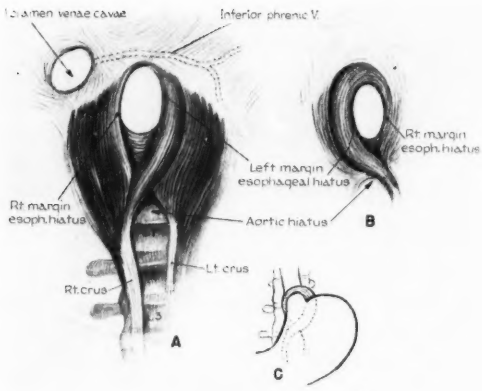


FIG. 2.

FIG. 1. Artist illustration of the inferior or abdominal aspect of the diaphragm drawn from a fresh cadaver specimen. The right crus, longer, thicker, and more tendinous than the left, separates into superficial and deep muscle bundles to form completely the esophageal hiatus. The superficial layer forms the right margin and the deep layer the left margin of the hiatal ring, effecting a sling-like arrangement of the fibers of the right crus. The close relation of the tendinous portion of the diaphragm and the inferior phrenic vein to the anterior angle of the hiatal ring is depicted.

FIG. 2. Artist interpretation of the anatomy of the esophageal hiatus drawn from a fresh cadaver specimen. A, The esophageal hiatus from the abdominal view. The formation of the hiatal ring or sling by the muscle fibers of the right crus is depicted. The greater length and width of the right crus compared to the left are demonstrated. B, The esophageal hiatus as it appears looking obliquely downward from the head of the cadaver specimen. The thick or deep layer of muscle fibers of the right crus which forms the left margin of the hiatal ring lies superficial to and crosses the superficial or thin layer of muscle fibers of the right crus which forms the right margin of the hiatal ring. C, Diagrammatic representation of the sling-like arrangement of the muscle fibers of the right crus of the diaphragm in the formation of the esophageal hiatal ring.

are retracted by guy sutures of fine silk (Fig. 3F, G). The horizontal portion of this incision extends medially (anteriorly) to the base of the pericardium, and laterally (posteriorly) to a point just beyond the thoracic aorta. The esophagus proximal to the hernial protrusion is mobilized by blunt digital dissection and encircled by a rubber tissue (Penrose) drain. With the maintenance of traction on the esophagus the hernia is mobilized by scissor dissection, and the whole of the hiatal muscular ring formed by the fibers of the right crus of the diaphragm is clearly defined (Fig. 4A, B). This step is considered a most essential part of the operation. A segment of the diaphragm in juxtaposition to the hiatal ring is tented by Babcock clamps and incised (Fig. 4C). The left index finger is inserted through this incision into the peritoneal cavity and through the esophageal hiatus into the hernial sac (Fig. 4C, D). The overlying layers, the phrenoesophageal ligament and the peritoneum, are elevated on the finger and separately incised (Fig. 4D, E). This procedure permits the entrance into the lumen of the sac and exposes the anterior wall of the stomach which forms the posterior wall of the hernial protrusion (Fig. 4F). If preferred, the hernial sac may be entered directly without first making the incision in the diaphragm.

The hernia is reduced either by traction through the diaphragm (Fig. 5A) or by downward displacement with the aid of a pledget of gauze in a ring clamp (Fig. 5C). If desired, both maneuvers may be used in combination. After reduction of the hernia the esophagus is displaced laterally (posteriorly) and the "crown" suture (No. 0 silk) is inserted medially (anteriorly) (Fig. 5B). This suture approximates the muscle fibers of the right crus which form the medial (anterior) angle of the hiatal ring. This angle is in juxtaposition to the to-

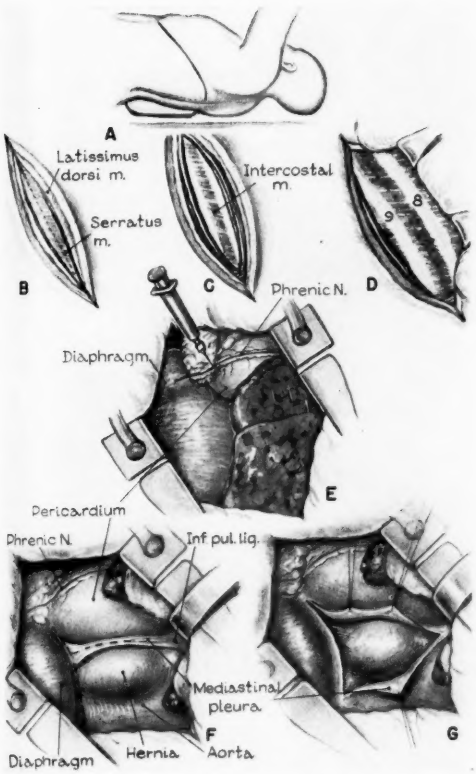


FIG. 3. A, The patient is placed in the right lateral prone position and the incision overlying the eighth interspace is outlined. B, C, D, The incision is deepened through the underlying muscle layers to expose the line of incision in the eighth interspace. E, The pleural cavity is entered and the wound margins are retracted. The phrenic nerve is not crushed but the diaphragm is paralyzed temporarily by injection of the nerve with 6 to 8 cubic centimeters of procaine (1 per cent) solution. F, The protrusion of the hernia in the esophageal triangle and the T-shaped incision in the mediastinal and diaphragmatic pleura are depicted. The esophageal triangle is bounded medially (anteriorly) by the pericardium and laterally (posteriorly) by the aorta. The base is formed by the diaphragm and the apex by proximal portion of inferior pulmonary ligament. G, Pleural flaps are retracted by silk guy sutures and extension of muscle fibers of diaphragm on base of hernial protrusion may be seen.

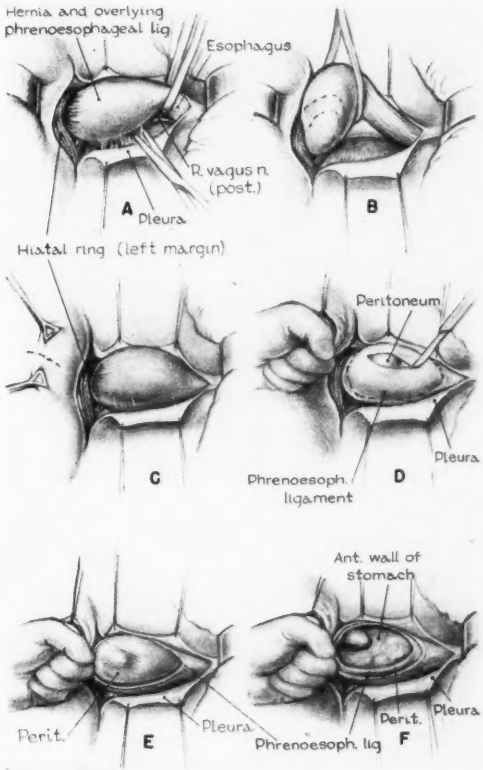


FIG. 4. A, The esophagus is encircled by a rubber tissue (Penrose) drain and with traction maintained the hernia is mobilized by scissor dissection. B, The mobilization is completed and the whole of the hiatal muscular ring formed completely by the right crus of the diaphragm (Figs. 1 and 2) is exposed. C, A segment of the diaphragm is tented by Babcock clamps and the site of incision is in dotted outline. D, The left index finger is inserted through the incision in the diaphragm and through the esophageal hiatus into the hernial sac. With the overlying structures tented on the index finger the phrenoesophageal ligament is incised to expose the underlying peritoneum which forms the anterior wall of the sac. The area to be excised is in dotted outline. E, F, Similarly the peritoneum is incised and the lumen of the sac is entered. Moreover, the posterior wall of the sac is formed by the anterior wall of the stomach, thereby constituting a sliding hernia.

dinous portion of the diaphragm and the inferior phrenic vein (Fig. 1). Accordingly, caution should be observed in the placement of the suture to avoid injury to the inferior phrenic vein. A second suture in this area may or may not be required. The esophagus is then displaced medially (anteriorly), and the lateral (posterior) sutures (No. 0 silk) are inserted. These sutures approximate not the right and left crura, as so commonly thought, but the superficial and deep muscle layers of the right crus of the diaphragm (Fig. 5C, D). In the approximation of the muscle layers of the right crus

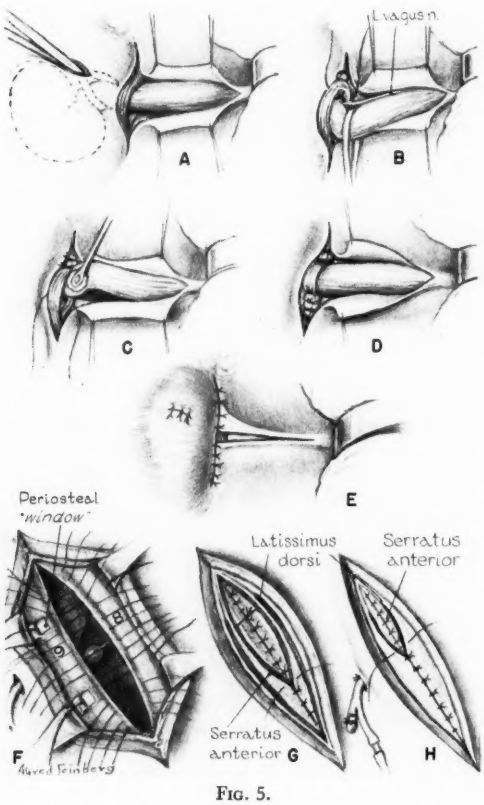


FIG. 5.

FIG. 5. A, By traction through the diaphragm the hernia is reduced. B, The esophagus is retracted laterally (posteriorly) and the innermost or "crown" suture is inserted. This suture approximates the muscle fibers of the right crus which forms the medial (anterior) angle of the hiatal ring and is in juxtaposition to both the tendinous portion of the diaphragm and the inferior phrenic vein (Fig. 1). C, D, The esophagus is displaced medially (anteriorly) and the lateral (posterior) angle of the esophageal hiatus is closed by approximating the muscle bundles of the right crus which form the right and left margins of the hiatal ring. In this approximation interrupted sutures of silk (No. 0) are used. E, The closure of the incisions in the diaphragm and the diaphragmatic pleura is completed. The incision in the mediastinal pleura is not sutured. F, G, H, Two pericostal sutures of silk (No. 3) are inserted and the wound is closed in layers with interrupted sutures of silk (No. 000). Water seal catheter (Foley 16F) drainage of the pleural cavity is routinely employed.

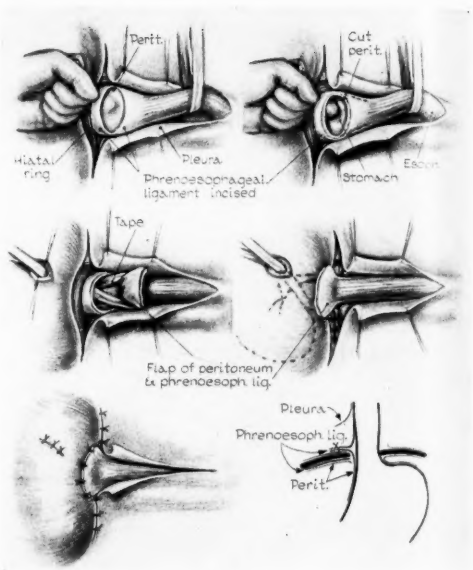


FIG. 6.

FIG. 6. Modification of the Allison method whereby the flap formed by the phrenoesophageal ligament and peritoneum proximally is sutured to the pleural rather than the peritoneal or under surface of the diaphragm. Technically it is simpler to do and is believed not to lessen the anchoring effect on the esophagus.

tension on the suture line is avoided. When completed the closure of the hiatal defect is snug but not too tight (Fig. 5D).

The incision in the diaphragm is closed and the flaps of diaphragmatic pleura are approximated by sutures of fine silk. The posterior mediastinal pleura is not sutured (Fig. 5E). A layer closure of the chest wall with water seal drainage of the pleural cavity completes the operation (Fig. 5F, G, H).

In 2 patients, only recently operated upon, the technique illustrated in Figure 6 was used. Basically, the principle of the operation is essentially the same as that of Allison. The main modification is that the cuff formed by the phrenoesophageal ligament and the peritoneum is sutured to the upper rather than to the under surface of the diaphragm. Technically this is simpler and is believed not to lessen the anchorage effect on the esophagus.

COMMENT

In a review of the various standard texts and atlases of anatomy and articles in the

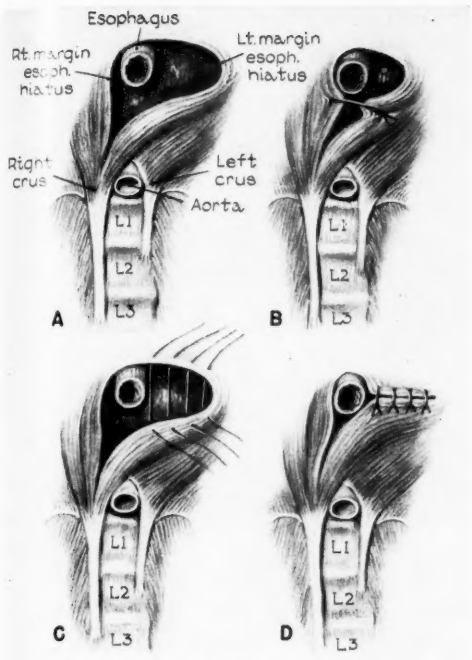


FIG. 7.

FIG. 7. A, Dilated esophageal hiatal ring prior to closure is demonstrated. The long axis of the ring is in a horizontal plane. B, The tension on the suture line and the inadequacy of closure on attempted approximation of the muscle layers of the right crus in a vertical plane posterior to the esophagus are shown. C, D, The muscle fibers of the right crus are approximated in a horizontal plane to the left of the esophagus. The closure is adequate and there is a minimum of tension on the suture line.

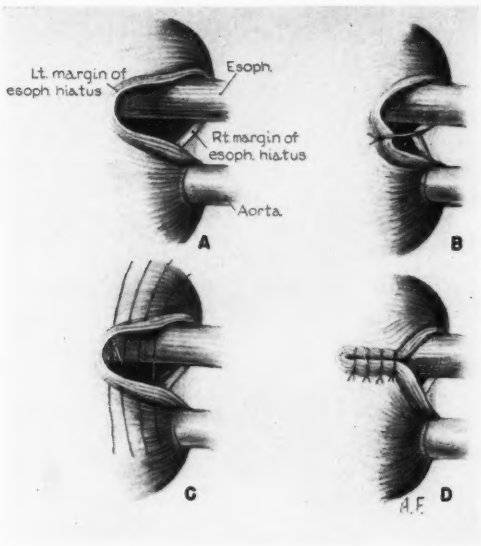


FIG. 8.

FIG. 8. The same illustrations as in Figure 7 when viewed from the upper or thoracic surface of the diaphragm with the patient in the right lateral prone position.

current surgical literature, one is impressed by the lack of uniformity relative to the description of the anatomy of the esophageal hiatal ring. Allison stated correctly that the hiatus for the esophagus was formed by the right crus of the diaphragm but this was not demonstrated clearly by appropriate anatomic illustrations. In the recent study of Carey and Hollinshead, the esophageal hiatus was formed by the right crus in 23 of 25 cadaver dissections. In the study herein presented the hiatus was formed solely and completely by the right crus of the diaphragm (Figs. 1 and 2). A knowledge of this basic anatomic characteristic is believed essential in planning any operation for repair of an esophageal hiatal hernia.

In the many descriptions of the technique employed in the operative repair of a hiatal hernia the approximation by sutures of the muscle fibers of the right and left crura is emphasized. In reality, however, one approximates not the crura but the margins of the right crus (Figs. 1 and 2). Theoretically, and based on pure anatomic considerations, as emphasized by Allison, the approximation should best be made in a vertical plane posterior to the esophagus. However, in some instances (Figs. 7A and 8A), the long axis of the enlarged hiatal ring is in the horizontal plane. Accordingly, if one should attempt to close the ring in a vertical plane behind the esophagus, the excessive angulation and tension upon the suture line (Figs. 7B and 8B) would preclude a satisfactory closure. Under such circumstances, the hiatal defect should be closed transversely (Figs. 7C, D and 8C, D).

In the surgical management of esophageal hiatal hernias, the particular type of closure

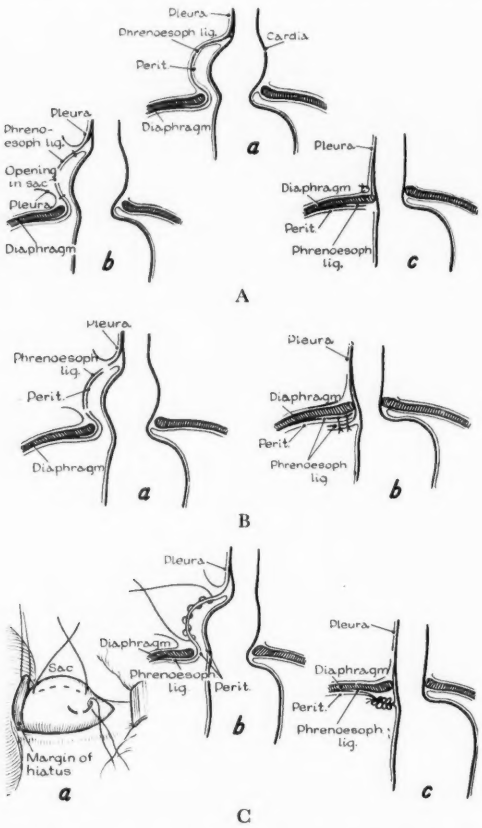


FIG. 9. Three methods of repair of a sliding hernia of the esophageal hiatus are depicted diagrammatically and in profile. A, a, The anatomic pathologic findings in a sliding hernia of the esophageal hiatus are demonstrated. b, c, The essentials in the method of repair of a sliding hernia as shown in the preceding artist illustrations are depicted. B, a, b, The Allison method. In this technique the importance of both the resuturing of the cut margin of the phrenoesophageal ligament to the under surface of the diaphragm and the closure of the hiatal defect in a vertical plane posterior to the esophagus is stressed. C, a, b, c, The method of Sweet. A series of longitudinal or circumferential plication sutures are inserted into the phrenoesophageal ligament and the peritoneum to invert and obliterate the sac. The closure of the lax muscle ring about the esophagus completes the repair of the hernia.

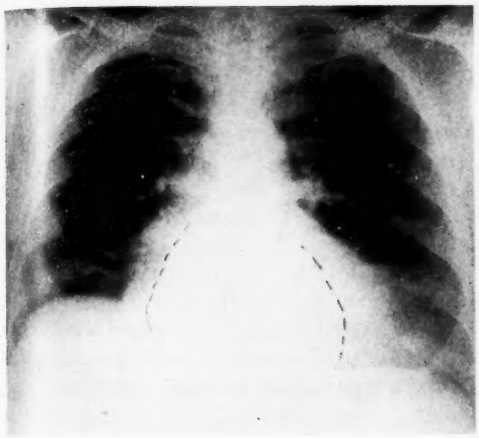
used should be predicated upon the findings at operation in the individual patient. In some instances, the closure in a vertical plane posterior to the esophagus may be preferred, whereas in others approximation of the margins of the right crus in a horizontal plane to either or both sides of the esophagus may prove the most satisfactory. The necessity for individualization relative to the type of closure has been demonstrated repeatedly at operation.

In the repair of the small and medium sized sliding hernias of the esophageal hiatus, Sweet has used effectively either circumferential or longitudinal plication sutures to invert and obliterate the sac (Fig. 9C). However, an incision into the lumen of the sac and the reduction of the sliding component, the anterior wall of the stomach, prior to the repair of the hiatal ring, is preferred.

Allison emphasized both the importance of suturing the proximal cut margin of the phrenoesophageal ligament to the under surface of the diaphragm (Fig. 9B) and the approximation of the muscle layers of the right crus in a vertical plane posterior to the esophagus. The resuturing of the phrenoesophageal ligament below the diaphragm, though anatomically correct, may be technically difficult. For this reason, the modification previously described (Fig. 6) is preferred. Furthermore, the suturing of the muscle layers of the right crus posterior to the esophagus may, in some instances, place undue tension upon the suture line (Figs. 7B and 8B) and preclude an adequate closure.

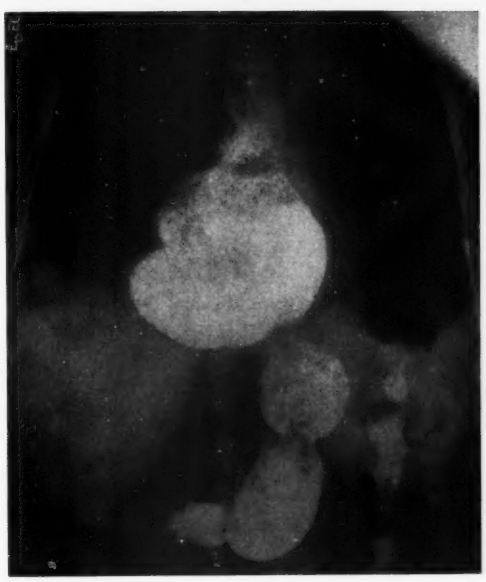
The choice of surgical approach, whether the transabdominal or transthoracic route, is one of preference of the surgeon. Suffice it to say, one should be familiar with both routes, the choice depending upon the findings in each patient. In general the transthoracic route is preferred.

In a discussion of esophageal hiatal hernias, the term "sliding," though correct by definition, is believed confusing. A sliding hernia defined is an irreducible hernia in which a portion of the wall of the sac is formed by the protruding viscus. With reference to sliding hernias of the esophageal hiatus, this would be the anterior wall of the stomach. In the inguinoscrotal area, it would be, either alone or in combination,



A

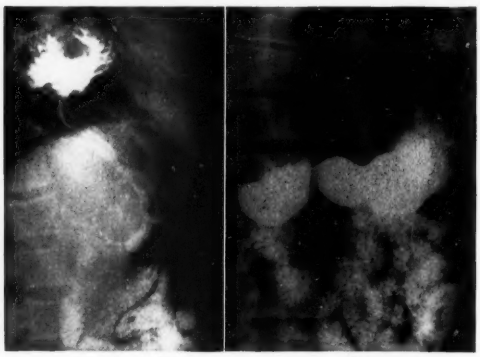
B



C

FIG. 10. A, Routine chest film in upright position with dotted outline indicating the area of double density within the cardiac silhouette caused by a huge sliding esophageal hiatal hernia. B, Roentgenogram in the erect position immediately after the ingestion of a small amount of barium. C, Roentgenogram in the erect position immediately following the ingestion of a full glass of barium. This shows the roentgenographic variation in the size of the hernia according to the volume of the barium ingested. It is the barium and not the hernia that "slides."

the sigmoid colon, the cecum, or the bladder. However, depending upon the anatomic location of the sliding hernia, there is a different connotation relative to the word sliding. In esophageal hiatal hernias it is commonly interpreted as meaning that the portion of the herniated viscus, namely, the stomach, slides in and out of the hernial orifice. However, the same meaning does not apply to sliding hernias of the inguinoscrotal region even though the anatomic pathologic basis in each is essentially the same. The reason for this dissociation of meaning, according to the anatomic location of the hernia, is believed based on the roentgenographic demonstration of variations in the size of esophageal hiatal hernias according to the position of the patient. This is thought more apparent than real and related to the ease of ingress and egress of barium within the herniated segment of the stomach. Under such circumstances, it is believed that the hernial sac and the segment of the anterior wall of the stomach which forms a component part of the wall of the sac do not slide but remain relatively stationary. In the author's opinion it is the barium that "slides" and it is the variation



A B

FIG. 11. Representative roentgenograms. A, Preoperative; B, postoperative.

in the volume of barium within the easily distensible herniated segment of the stomach that usually accounts for the roentgenographic variation in the size of sliding hernias of the esophageal hiatus (Fig. 10B, C). This reasoning is substantiated by the fact that at operation, either from below or above the diaphragm, and regardless of the position of the patient, a spontaneous reduction of a sliding hernia of the esophageal hiatus has not been observed. Contrariwise, the reduction of the hernia and the maintenance of its reduction may at times be most difficult. Finally, the frequency and the ease with which unsuspected sliding hernias of the esophageal hiatus are demonstrated on routine roentgenograms after a barium meal, and with the patient in the erect position (Fig. 10B, C), further attest to the stationary rather than to the "sliding" qualities of sliding hernias of the esophageal hiatus.

Similarly, the variation noted in the clinical manifestations of hiatal hernias, dependent upon the degree of filling of the stomach and the posture of the patient, is believed related to the ease of ingress and egress of the gastric contents into the herniated segment and not due to the "sliding" of the hernia.

In support of this reasoning, Allison stated: "When a sliding hernia has once occurred, the elastic recoil of the esophagus, together with the positive abdominal and negative thoracic pressures, tend to keep the cardia in the mediastinum at all times." Nevertheless, in some patients, the same author noted variations in the position of the cardia relative to the level of the diaphragm. This was demonstrated by applying silver clips (Cushing) to the mucosa of the cardia through an esophagoscope and then obtaining serial roentgenograms to show variations in the position of the clips from a level below to a level 2 to 3 inches above the diaphragm. However, one may question the exactness of this method in determining the position of the cardia.

CONCLUSIONS

The hiatus of the diaphragm for the esophagus is in general formed solely and completely by the right crus of the diaphragm. In the surgical correction of esophageal hiatal hernias the muscle fibers of the right crus only are sutured. The choice of operative approach, either transabdominal or transthoracic, is dependent upon the particular findings in each patient and the preference of the surgeon. In general, the transthoracic route is preferred.

The variations in the size of sliding hernias of the esophageal hiatus demonstrable roentgenographically are believed due to the ease of ingress and egress of barium within the distensible herniated segment of the stomach and to the volume of barium ingested rather than an actual sliding motion of the herniated viscus.

REFERENCES

1. ALLISON, P. R. Reflux esophagitis, sliding hiatal hernia, and the anatomy of repair. Surg. Gyn. Obst., 1951, 92: 419–431.
2. CAREY, J. M., and HOLLINSHEAD, W. H. An anatomic study of the esophageal hiatus. Surg. Gyn. Obst., 1955, 100: 196–200.
3. SWEET, R. H. The repair of hiatus hernia of the diaphragm by the supradiaphragmatic approach. N. England J. M., 1948, 238: 649.

THE TREATMENT OF CAUSTIC STRICTURES OF THE ESOPHAGUS

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DURING the 6 years from July 1948 to July 1954, 208 patients with caustic soda injuries have been admitted to our wards. The sociologic aspects of caustic poisoning have already been discussed (7) as has the diagnosis and treatment of acute caustic soda poisoning (8). A recent communication on the clinical aspects of corrosive strictures and their evaluation was based on an experience of 133 cases with injuries due to caustic soda and 14 due to other corrosives (9). The present paper deals with our management of these 147 cases during the period of the past 6 years.

Satisfactory treatment must be based upon a thorough evaluation of the severity of the stricture and for this purpose it is convenient to grade the strictures according to their length and density:

Grade 1. Fibrosis is circumscribed, being confined to less than the total circumference of the esophagus and to a short segment in length. These are shelf strictures and they never cause significant narrowing of the lumen.

Grade 2. These are localized annular strictures involving the total circumference of the esophagus. The fibrosis does not penetrate beyond the submucosa and consequently narrowing is never pronounced and treatment never a difficult problem.

Grade 3. These are dense strictures of limited length (arbitrarily less than ½ inch long). Fibrosis extends through the outer muscular coats, and perhaps the lumen, which is lined by epithelium, may be reduced to a thread.

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Grade 4a. These are strictures of more than half an inch length which have little tendency to progressive narrowing. The subgrade is judged by the fact that dilatation is easy and the lumen maintains its stretched caliber. Fibrosis is confined essentially to the mucosa and submucosa. The stricture is lined by epithelium, regeneration having occurred from surviving islands of mucosa.

Grade 4b. These tubular strictures have densely fibrotic walls, periesophageal adhesions, and marked luminal narrowing. Because of the extensive destruction epithelium cannot rebridge the gap and the lumen is lined by fibrous and granulation tissue. Such strictures are always found to be difficult to treat.

In our experience approximately 50 per cent of all patients admitted with acute caustic soda poisoning develop esophageal strictures. This does not imply that corrosive burns of the esophagus may heal completely but rather that in half the cases the corrosive never enters the esophagus.

Isolated injury is unusual. There were only 21 (14 per cent) solitary grade 1, 2, or 3 strictures and these followed the ingestion of small amounts of dilute corrosive. The brunt of the injury is usually borne by the retrocardiac portion of the gullet and here grade 4 strictures are common. In this series 72 cases (48 per cent) had grade 4b strictures and in only 4 instances were these sited mainly in the upper esophagus. However, even though the lower esophagus is the most severely affected it is usual for fibrosis to involve the upper gullet as well. We now view severe injuries as an affection of the whole esophagus, for even the apparently normal areas usually demonstrate considerable sub-

epithelial fibrosis upon microscopic section (Fig. 1).

There have been 14 cases with associated gastric fibrosis, 10 due to caustic soda and 4 due to hydrochloric acid. In 13 of these, symptoms of gastric obstruction were present. The incidence of pyloric stenosis following hydrochloric acid ingestion is very high. We have seen 5 cases, in 4 of which this complication developed (9).

THE PROBLEMS OF TREATMENT

Until recent years the management of benign strictures of the esophagus was the prerogative of the endoscopist for the surgical extirpation of the gullet presented such difficulties and dangers that it was seldom attempted. With recent technical advances in surgery, anesthesia and chemotherapy esophageal surgery has become commonplace and it is no longer necessary to persist interminably with futile and dangerous endoscopic techniques. Apart from the accidents due to inexperience, most fatalities in the past have resulted from the belief that only the bougie can avoid the discomfort of a permanent gastrostomy. Today, however, there is a tendency for the pendulum to swing the other way and the adventurous surgeon who embarks hastily upon esophagectomy is as great a menace as the esophagoscopist who is unshakably determined to succeed by bouginage.

It is impossible to decide from an x-ray picture alone what form of treatment is indicated. It is necessary that the surgeon be aware of the inherent characteristics of the stricture, the site, length, fixation, the narrowness and tortuosity of the lumen, the resistance offered to attempts at dilatation. Here, even more than with most surgical problems, the case has to be judged as a whole and the temperament of the patient has always to be considered. The cardinal rule in treatment is never to make a hasty decision. Starvation, due to neglect or food impaction, is the only urgency and this condition can always be countered by enterostomy or removal of the obstructing bolus.

MAINTENANCE OF NUTRITION

No matter what the eventual treatment many weeks will pass before a patient with severe esophageal stricture is again able to swallow normally. Under these circumstances the only alternative to oral feeding is through a gastrostomy or jejunostomy. Fifty-eight of our patients have had one of these operations at some stage of treatment, 52 of whom had grade 4b strictures. Only 1 of the 6 patients with lesser strictures was operated upon in our unit and this was because of instrumental perforation of the esophagus.

INDICATIONS FOR ENTEROSTOMY

1. Persistent severe dysphagia notwithstanding attempts at dilating the stricture. When an enterostomy is needed within 4 weeks of corrosion the esophagus is so seriously damaged that dilatation is seldom effective in controlling the stricture. Of the 35 patients who had early enterostomies 33 were ultimately subjected to esophagogastrostomy and 2 died from the effects of their injuries.

2. Instrumental perforation of the esophagus. This happened on 4 occasions.

3. Childhood, mental defect, and inability to co-operate in self-bouginage when frequent dilatations over a long period of time are necessary.

THE CHOICE OF ENTEROSTOMY

The patient may have to rely upon the enterostomy for many months and, therefore, it is necessary that the following criteria be met:

1. The enterostomy tube must be of sufficiently wide bore to allow thick concentrated foods to be administered.

2. It should be possible to remove and reintroduce the tube without particular difficulty.

3. Reflux of intestinal contents around the tube should be minimal so as to avoid excoriation of the skin.

Witzel jejunostomies were done in 2 early cases but this operation is unsatisfactory be-

cause of the narrowness of the tube and the difficulty of reintroduction should temporary removal of the tube be necessary. On 6 occasions a Roux-Y jejunostomy was done because corrosion of the stomach precluded gastrostomy. Apart from an instance of retrograde intususception this operation has been fairly satisfactory but whenever possible a gastrostomy is preferred. Patients with jejunostomies are peculiarly susceptible to attacks of enteritis and intolerant of the rich high calorie feeds. Attacks of diarrhea are common and digestion of food is often incomplete so that patients fail to gain weight satisfactorily. A gastrostomy is less difficult to manage and diarrhea, though not infrequent during the early stages, is never as intractable as that which occurs with jejunostomies so that satisfactory gain in weight is usual. The theoretical disadvantage that adhesions would subsequently hinder gastric mobilization has, in practice, been found to be slight. The routine gastrostomy, the Kader-Senn type of "ink-well" operation, has proved generally suitable.

One patient died from peritonitis following a jejunostomy performed distal to a gastroenterostomy. He had a grade 4b stricture with pyloric stenosis and died 28 days after operation. Vinson reports a mortality rate of 10 to 25 per cent after gastrostomy but this was in the preantibiotic era. Our 1 death is a reminder that the operation should still be undertaken with maximum attention to details of technique and asepsis.

Dysphagia often lessens considerably after gastrostomy, a fact noted by Hodge and Scharfe in 1937. This occurs particularly with patients who have been subjected to frequent dilatations and probably is due to subsidence of edema and spasm caused by repeated instrumentation.

DILATATION

A great deal has been written on the treatment of esophageal strictures by dilatation. Many of the methods described are thinly veiled copies of previous techniques and few have stood the test of time. Methods which entail forcing a passage under screen control or by combined peroral and retrograde esophagoscopy are no longer justified. Vinson had 3 deaths out of 7 so treated and Tucker quotes a mortality of 50 to 75 per cent. Dilatation still remains the sheet anchor of treatment but there are definite indications for and against its use.

FIG. 1. Biopsy of esophagus taken from the site of anastomosis of stomach to esophagus. This site had been chosen because the esophageal wall seemed normal from without. Section shows considerable submucosal fibrosis. Magnification ×28.

INDICATIONS FOR DILATATION

The grade of stricture. Grade 1, 2, 3, and 4a strictures can all be treated successfully by dilatation though occasionally the two higher grades may provide some difficulties. Grade 4b strictures are always difficult to manage but dilatation should be attempted unless otherwise contraindicated.

The response to dilatation. It is our practice to dilate strictures at weekly intervals under general anesthesia and this provides the opportunity of assessing progress. When succes-

sive examinations confirm that the stricture admits progressively larger bougies the prognosis is hopeful. It is the ability of an established stricture to maintain a dilated lumen that is the crucial factor. When repeated attempts fail to effect advance, dilatation should be abandoned.

The age, intelligence, and temperament of the patient. Minor and moderate strictures can be controlled by weekly dilatations but grade 4b strictures require more frequent bouginage. Daily anesthetics are patently undesirable and it is, therefore, an advantage to start self-bouginage as soon as possible. It has been difficult to persuade children to do this and occasional adults have failed to co-operate. In such cases, the chances of success by conservative means are considerably lessened.

INDICATIONS FOR ABANDONING DILATATION

Persistent ulceration. Patients with acute corrosive injuries are examined by esophagoscopy within a week of admission to determine whether the gullet has been involved (8, 9). If corrosion is found the examination is repeated at weekly intervals until healing has occurred or until the stricture face has epithelialized. At this stage an appropriate-sized well lubricated bougie is gently passed through the stricture to estimate the caliber of the lumen. The bougie is then withdrawn and is examined for blood. In the absence of blood-staining dilatation is begun, but its presence denotes that the epithelium has not regenerated and ulceration persists. With mild injuries it may be possible to start dilatation within 2 weeks of poisoning but with severe damage the stricture may be so narrowed that a gastrostomy is needed before dilatation can be commenced. Should ulceration persist longer than 6 weeks the chances of success are small.

Poor response to dilatation. It is not our experience that so long as a lumen exists the stricture can always be adequately dilated. To restore normal swallowing a lumen corresponding to a size 22 bougie must be maintained though reasonably comfortable swallowing is possible if a size 16 bougie is admitted. If persistent efforts at dilatation fail to attain this minimum caliber the attempts should be abandoned.

Impermeable strictures. There may once have been some justification, on the grounds of the occasional success, for heroic attempts at re-establishment of esophageal patency by instrumental means when an impermeable stricture was present but today this no longer exists.

There have been 14 strictures in which it was impossible to negotiate the obstruction with bougie or string. In 2 this was due to a total obstruction and in the remainder to extreme tortuosity of the narrowed lumen. In these cases dilatation is fraught with dangers and should not be attempted. Our practice of passing a fine bougie from an early stage has greatly lessened this complication (9).

TECHNIQUE OF DILATATION

Three methods of bouginage have been used: (1) peroral esophagoscopic dilatation; (2) retrograde dilatation; and (3) self-dilatation.

Peroral esophagoscopic dilatation. It is always wise to study the esophagograph before attempting to dilate an unfamiliar stricture, for this may show tortuosity or irregularity which influences one's approach. Dilatation is controlled entirely by the sense of touch and only gentle pressure is permissible. On the first few occasions dilatation should be limited to 3 sizes larger than the first bougie to be palpably gripped by the stricture, but once successfully negotiated the risk of perforation decreases and subsequent progress may be as rapid as the stricture permits. With grade 4b strictures progress is often slow and it is tempting to overdilate but the impulse should be rigidly opposed.

Occasionally, rapid shrinkage of the dilated lumen may be due to elasticity of the stricture and not to dense fibrosis. We have experienced this with localized strictures when on removal of the bougie the stricture immediately reverted to its original caliber.

In these cases the whole circumference of the stricture should be punched out so that it may be converted into a more callous structure.

Retrograde dilatation. Retrograde dilatation of esophageal strictures was employed by Ehrlich in 1897, and since that time the method has often been revived. Billroth pointed out that the dilated esophagus above the stricture was bowl-shaped, whereas it was funnel-shaped below, so permitting a bougie to pass naturally into the stricture lumen situated at the apex of the funnel. The retrograde route has been considered preferable for this reason and also because it does not necessarily require anesthesia or hospitalization. Tucker revived the technique and designed a set of 13 bougies ranging in size from No. 10 to 34 French for the purpose. He advised that dilatation be started 3 weeks after gastrostomy so as to allow the abdominal wound to heal and that in the interim the patient swallow a length of braided silk which is recovered through the gastrostomy opening. The dilators are tied to the string protruding from the gastrostomy and, by pulling on the end of the string at the mouth, are drawn into the stomach and through the esophagus. After each operation the bougies are detached, the gastrostomy and oral ends of the thread are tied together, and the gastrostomy tube is replaced. Tucker advises that effective dilatation be limited to 3 sizes of bougie on each occasion. The operation should be performed daily and should, if possible, be done by the patient himself. If the patient is unable to swallow a string it is usually possible to introduce a small esophagoscope through the gastrostomy and to pass a fine bougie through the stricture from below. The thread is then tied to the tip of the bougie presenting in the mouth and is pulled through the stricture when the bougie is withdrawn.

Dilatation from below is a safe and relatively simple maneuver but we have only used it with severe grade 4b strictures when dysphagia has been sufficiently severe in itself to warrant a gastrostomy. Thirteen patients, 6 children and 7 adults, have been treated in this way. They all had very tight strictures which, for one or other reason, were not dilatable by the antegrade route. In only 4 instances was the treatment successful in establishing an adequate lumen but this is more a commentary on the severity of the strictures than on the inadequacy of the method. The only complication was on one occasion when the stomach with the parietal peritoneum was detached from the posterior rectus sheath and, though no active reparative measures were necessary, it was thought advisable to abandon the treatment.

FIG. 2. Double grade 4b stricture of the esophagus. A false passage has been produced at the site of the upper stricture.

Retrograde dilatation is a useful adjunct to the treatment of strictures and can be used

with advantage whenever a gastrostomy has had to be done, but a carefully performed antegrade dilatation is effective in most moderate cases and consequently the retrograde route has had a limited application in our hands.

Self-dilatation. Though it is possible to effect active dilatation by self-bouginage we have used it primarily to maintain an already dilated lumen. As soon as an adequate lumen has been attained under general anesthesia the patient is instructed to swallow a bougie himself. Ideally a size 24 bougie should be swallowed but anything above a size 20 is satisfactory. No force should be used in handling the instrument and it must be passed to its full extent so as to traverse the whole stricture. The maneuver is repeated twice daily and the bougie should be retained in position for several minutes. As soon as the patient is proficient in the technique he is allowed home to continue the routine and after 1 month, if all is well, bouginage need only be performed once daily. After 6 months it is probably safe to permit the patient to pass the bougie once weekly. As some patients tend to get careless we insist that they visit us at regular monthly intervals to swallow the bougie in our presence. This continues for a year, after which they attend at 3 monthly intervals.

Most patients persevere with their rather unpleasant routine but occasionally one will defect when beyond surveillance. Inevitably dysphagia recurs and the whole procedure has to be repeated. Some patients are never able to swallow a bougie and remain for long periods in the hospital undergoing repeated esophagoscopic dilatations.

COMPLICATIONS OF DILATATION

Instrumental dilatation of the esophagus should only be undertaken by those well versed in the technique and conversant with the dangers. It is particularly foolhardy for an inexperienced operator to attempt the first dilatation as this is the time when mishaps most commonly occur. Apart from inexperience the usual cause of accidents is overpersistent attempts at establishing a lumen through a dense stricture.

There have been 2 fatalities due to attempts at dilatation and the following complications have been encountered: (a) acute dysphagia; (b) hemorrhage; (c) production of false passages; (d) perforation into the pleura; (e) mediastinitis.

Acute dysphagia. Intensification of dysphagia is not an uncommon sequel and indicates that reactive edema due to excessive dilatation has been produced. Difficulty may be very pronounced and may last for 4 to 5 days.

Hemorrhage. Blood staining of the bougie after dilatation implies the persistence of ulceration or overenergetic instrumentation. As far as possible this should be avoided by gentleness in technique though hemorrhage from these causes is seldom severe. There have been 2 cases of alarming overt hemorrhage, one fatal, and a further fatal case of hidden hemorrhage.

The 2 patients who had massive hematemeses after dilatation had grade 4b strictures, the one of several months standing the other a developing stricture only 4 weeks after corrosion. Neither were particularly difficult operations and the vomiting of blood started some hours after recovery from the anesthetic. The first vomited about 2 pints of blood over the course of 2 days and was treated conservatively. Three weeks later dilatations were recommenced without mishap. The second patient was practically exsanguinated by her first hematemesis and had to be urgently transfused with 6 pints of blood. A massive melena recurred next day and after much discussion as to the origin of the hemorrhage it was decided to do a laparotomy, with the object of opening the stomach and packing the esophagus from below. At operation the stomach was distended with blood clot and when this was evacuated through a wide incision a large submucosal hematoma was seen on the greater curve 4 inches from the cardia in the middle of which was a freely bleeding puncture wound. It was estimated that a

bougie projected through the esophagus could have struck the stomach wall at this site. The vein was underrun with a stitch and the stomach and abdomen closed but the patient never recovered consciousness and died some hours later. Necropsy confirmed the absence of any other cause for the hemorrhage. It is considered that both these cases of hemorrhage were due to rupture of gastric veins caused by inserting the bougie too vigorously through the stricture into the stomach.

The second death was due to mediastinal hemorrhage caused by a split in the fibrosed stricture wall which had involved a large mediastinal vein. After a difficult first dilatation the child was pale and shocked without apparent cause and notwithstanding treatment died next day. The diagnosis was established at necropsy.

False passage. We have seen 3 blind false passages produced by dilatation (Fig. 2). All were severe grade 4b strictures and the tracks were probably made during the first dilatation. There is a particular danger of this complication when dilating a stricture with a tortuous lumen.

Perforation into the pleura. Four cases of perforation of a strictured esophagus have been treated and on each occasion rupture had occurred into the right pleural cavity. This tendency for perforation to involve the adjacent pleura is probably due to obliteration of the periesophageal tissue planes so that the perforating bougie plows its course without being deflected by the fascia. The accident invariably follows a difficult blind dilatation of a tight or tortuous stricture and the complication should be suspected whenever the patient complains of lateral chest pain after such an operation. In each case pneumothoraces developed only after 48 hours, a fact which considerably delayed the correct diagnosis. It would seem wise, therefore, to perform a lipiodol swallow examination whenever the complication is suspected and indeed 1 case was recognized early by this means. The delayed development of the hydropneumothoraces may be due to the fact that the tight strictures and the narrow perforation tracks allowed very little air or fluid to enter the pleural cavity from the esophagus.

FIG. 3. Left cervical esophagogastrostomy showing the remnant of the strictured esophagus and the absence of narrowing at the thoracic inlet even though the first rib and clavicle have been left intact.

Owing to the delay in diagnosis and particularly as the esophagi were severely diseased it was not considered wise to repair the fistulas and they were all treated by closed intercostal drainage, gastrostomy, and antibiotics. In 2 instances this was curative while the others developed empyemas which required open drainage. In every case the esophageal perforation closed spontaneously and permanently.

Mediastinitis. On 4 occasions fever, increased dysphagia, and persistent severe back pain have followed difficult dilatations. These patients were ill for several days but recovered on intensive antibiotic treatment. Though there is no final proof of the exact

cause of these symptoms they were probably due to mediastinal infection arising from a tear in the stricture wall.

The manifestations of this complication of esophageal rupture are modified by the mediastinal fibrosis which accompanies strictures most liable to perforation. Surgical emphysema and radiologic broadening of the mediastinum are absent because the fibrosis does not allow exudates to accumulate, while obliteration of the normal anatomic planes prevents air from tracking upward into the neck.

THE SURGICAL TREATMENT OF CORROSIVE STRICTURES

As soon as it becomes obvious that the antegrade dilatation holds no further prospects of success the treatment should be abandoned and gastrostomy feeding instituted. It is of paramount importance that all candidates for esophagogastrostomy should be given adequate gastrostomy feeds, for months if necessary, in an effort to regain their normal weight. This preoperative period should never be hurried and the patient should be fully aware of its importance.

Forty patients with grade 4b strictures have had the operation, few if any of whom could possibly have avoided it had they been determined to succeed by dilatation. Twenty-seven with grade 4b strictures (35 per cent of all grade 4b strictures) have controlled their strictures by virtue of their persistence and determination to swallow a bougie, but it is possible that some may yet abandon the struggle and have to be operated upon. Three patients, who have had esophagogastrostomies, had endeavored for more than a year to control their strictures by self-bouginage.

The various techniques which have been used when operating on the earlier cases in this series have been described in a previous paper (6). The multiple staged extrathoracic operations described by Bircher, Beck, and Yudin have not been attempted because of their numerous complications which multiply with each stage of the reconstruction. All our patients have had transthoracic operations the first 10 being done through the right chest but in one stage as advocated by Tanner. Since then, apart from 3 further cases done in this manner, the stomach has been mobilized through a left thoracic or abdominothoracic incision and the anastomosis performed either through the same intercostal incision (1 case), through a separate intercostal incision (9 cases), or in the neck through a separate cervical exposure (17 cases). In every case the anastomosis has been performed above the level of the aortic arch. The strictured esophagus has never been excised and no complication has arisen from this source. It is believed that the addition of esophagectomy in the presence of dense periesophageal adhesions makes the operation more formidable and shocking to the patient.

Since we have come to view severe esophageal strictures as an affection of the whole esophagus we have done more esophagopharyngostomies. Intrathoracic anastomoses were so frequently followed by stricturing at or above the anastomosis and biopsies from the apparently normal esophagus at these sites so consistently showed fibrosis (Fig. 1) that the policy of going higher was forced upon us. The operation now favored can be undertaken by two surgeons operating simultaneously, as thus the surgeon who has mobilized the stomach is able to adjust the lie and tension of the stomach while the cervical anastomosis is being done. It has never been found necessary to remove the first rib or the clavicle as advised by Sweet for there always seems to be ample space (Fig. 3). It is usually possible to mobilize sufficient stomach to effect a comfortable anastomosis in the neck but if there is a fear of excessive tension on the anastomosis the stomach should be fixed to the cervical fascia and cervical esophagostomy and gastrostomy should be done. At a second stage a plastic junction can be effected. This has now been done on 3 occasions.

Thirteen of the 14 patients with gastric fibrosis required operation for symptoms of

pyloric obstruction. These symptoms invariably start early and laparotomies have been done in every case within 6 weeks of corrosion. Seven of the 9 caused by caustic soda and all 4 caused by hydrochloric acid had pyloric stenosis and 2 due to caustic soda had diffuse gastric fibrosis, though in 1 case it was possible to treat it as a case of pyloric stenosis. In 12 cases, therefore, gastroenterostomy with either gastrostomy (6 cases) or jejunostomy (6 cases) was performed and in 1 case a jejunostomy without gastroenterostomy. This last patient was eventually treated by esophagojejunostomy because of the gastric fibrosis and represents the only such operation in this series.

All these patients had in addition esophageal strictures of greater or lesser severity, and in 6 cases it was possible to treat them successfully by dilatation. When doing a gastroenterostomy on a patient with a developing grade 4b stricture it is advisable to do a long loop antecolic operation and an enteroanastomosis. In the first case in which this precaution was neglected the patient developed a high intestinal obstruction because the afferent loop was stretched and acutely kinked when the stomach was drawn upward into the chest at the second operation and had to be treated by emergency enteroanastomosis.

Three patients with localized grade 3 strictures, 2 of the cervical esophagus and 1 of the thoracic esophagus, have been treated by excision of the stricture and reanastomosis of the esophagus. One operation was completely successful but in the others, strictures recurred. These were done in the early years of this series but because of our present knowledge of the widespread nature of fibrosis in this condition and of the inevitable success of dilatation for isolated stricture we no longer attempt local operations.

RESULTS OF OPERATION

There have been 8 deaths after operation, a mortality rate of 20 per cent. This high figure is due largely to initial inexperience with the snags and pitfalls which are presented by corrosive strictures. With increased familiarity our results have improved considerably and in the last 20 cases we have had 2 deaths (10 per cent).

FIG. 4. Right esophagogastrostomy. The junction had been made into an area of esophageal fibrosis and the stoma has strictured. Barium has entered the stomach through the strictured esophagus. A second operation of cervical esophagogastrostomy has been successful.

One child died on the table during mobilization of the stomach and before the chest had been opened, and 2 further patients never recovered consciousness. These were among the first 6 operations and with improved preoperative care and increased experience on the part of the anesthetists there have been no further "anesthetic" deaths. It is significant that in 2 of these patients we had relied upon preoperative intravenous therapy to restore their nutritional state. As a result of these disastrous experiences, surgery is never contemplated until the body weight has approached normal by enterostomy feeding, and it has been necessary to delay as long as a year before considering a patient fit to undergo the operation. A further patient died on the fourth day after operation and no gross cause was

FIG. 5. Right esophagogastrostomy in which the stoma was deliberately placed below a widely patent cervical stricture. Narrowing has progressed and the patient now requires occasional bouginage.

found at necropsy. This death as well has been ascribed to inefficient preoperative treatment.

Four patients died from 3 to 6 weeks after operation. In 2 instances the anastomosis disrupted during the second week, empyemas developed and feeding became a desperate problem. Attempts to reconstitute the anastomosis failed and the patients died miserably. The disruption of an intrathoracic anastomosis is a disastrous complication but a similar mishap in the neck is of far less import so it is wise to insert a drain down to the anastomosis whenever a cervical junction is effected so that, should disruption occur, drainage will be to the outside.

The other 2 fatal cases presented identically disastrous pictures but in these cases gastric perforations remote from the site of anastomosis were the cause. Both patients had had cervical operations and perforation occurred during the second week. Notwithstanding attempts at late closure of the defects the patients eventually died after the perforations had recurred. At necropsy these were seen to be remote from the anastomosis as well as from the sites of the closed gastrostomy.

COMPLICATIONS OF OPERATION

In 24 cases restitution of swallowing ability has been complete, and the patients have been able to return to normal life though 2 have required second operations before this ideal has been attained. The remaining 8 survivors require to pass occasional bougies in order to control high cervical or stomal strictures. The reasons for unsatisfactory results have been:

1. Anastomosis made at site of esophageal fibrosis (Fig. 4). When fibrosis has not extended beyond the esophagus it may be difficult to detect the presence of a stricture from the outer aspect. It is therefore essential to choose and mark the site of anastomosis as the first step of the operation by packing the pharynx and normal esophagus through an esophagoscope. Even so, the junction may be effected into a fibrosed segment which may subsequently contract. An esophagopharyngostomy should be performed if there is the slightest suspicion of high esophageal fibrosis.

2. Anastomosis below an area of fibrosis. On 3 occasions the anastomosis was deliberately placed below an area of fibrosis in the belief that the operation would thereby be somewhat quicker and easier. This is false economy for the chances of progressive narrowing of the higher stricture with a disappointing end result are great (Fig. 5).

3. Peptic esophagitis. There have been 2 cases in which acid regurgitation has been a complaint after operation. One of these patients has subsequently developed a proxi-

mal stricture but whether this is a residue of corrosion or an effect of the reflux is difficult to decide. It seems that with high esophagogastrostomies reflux of gastric contents is not a great hazard.

4. Gastric ulceration. Apart from 2 fatal cases previously mentioned, there has been a further case of gastric ulceration. Thirteen months after the esophagogastrostomy a colored woman, when 7 months pregnant, had a large hematemesis. Gastroscopy showed a greater curve ulcer 3 inches beyond the stoma. She was treated medically and has been well since. Brooks and Stafford reported 2 fatal gastric perforations within a month of esophagectomy and gastroesophageal anastomosis. Nuboer also had 2 cases, 1 fatal within 2 weeks of operation and the other occurring 2½ years later and successfully treated by surgery. Merendino and Emerson had 2 fatal cases within a month of operation and they found that the ulcers were centered on sutures placed so as to fix the stomach to the chest wall. Nuboer suggested that vagotomy may be a factor because of the reports of Orr and Johnson and of Dragstedt, Camp, and Fritz who noted gastric ulceration following vagotomy for duodenal ulcer.

SUMMARY AND CONCLUSIONS

One hundred and forty-seven cases of corrosive strictures of the esophagus have been treated in 6 years.

Seventy-two grade 1, 2, 3, and 4a strictures and 27 grade 4b strictures have been controlled by dilatation. A total of 99 cases (70 per cent) have, therefore, been successfully treated in this way.

There were 72 grade 4b strictures of which 40 (55 per cent) have been treated by esophagogastrostomy (1 by esophagojejunostomy) after dilatation had failed.

Two patients have died as a result of accidents of dilatation. There have been 2 further deaths from inhalation bronchopneumonia while the patients were under treatment by dilatation and 1 which followed a jejunostomy. The mortality rate for the whole series has therefore been 9 per cent (13 cases). We have already reported a 5 per cent mortality rate for patients with acute corrosive injuries (8). Of the 72 patients with grade 4b strictures, 34 came under our care at the time of their original injury and 38 were referred to us either because dilatation had failed or because of some complication of dilatation. Among the patients treated by us from the onset 14 have had esophagogastrostomies (41 per cent) whereas 26 of the referred patients eventually required it (70 per cent). It is believed that this significant comparison is due to the early care which our patients received (8).

Corrosive stricture of the esophagus is a serious disease. In this series 9 per cent have sooner or later died because of it. The outlook is, however, far less gloomy than it was a half century ago when Witthaus in 1911 and von Hacker in 1899 reported mortality rates of 34 and 35 per cent respectively. The improvement is chiefly due to the introduction of antibiotics but also in part to the extraordinary advances in anesthesia and, we like to think, to the development of thoracic surgery which salvages those patients with severe esophageal strictures who would either die or be condemned to permanent gastrostomy. And yet there is really so little cause for complacency; this is a disease which we should never have to treat for it is the needless product of a society which continues to permit the free sale of caustic soda at a time when inexpensive and harmless detergents are readily available.

REFERENCES

1. Beck, K. Muenchen U. Wiesb., 1922, 82: 37.
2. Billroth, C. A. Allg. Wien. med. Ztg, 1883, 28: 141.
3. Bircher, E. Zbl. Chir., 1907, 34: 1479.
4. Brookes, V. S., and Stafford, J. L. Peptic ulceration and perforation of stomach after oesophagectomy. Thorax, Lond., 1952, 7: 167–169.
5. Dragstedt, L. R., Camp, E. H., and Fritz, J. M. Recurrence of gastric ulcer after complete vagotomy. Ann. Surg., 1949, 130: 843–854.
6. Fatti, L., Crawshaw, G. R., and Marchand, P. Technique of high oesophago-gastric anastomosis. S. Afr. M. J., 1952, 26: 741–748.
7. Marchand, P. Caustic soda poisoning; the sociological aspect. S. Afr. M. J., 1954, 28: 415–419.
8. Idem. Acute caustic soda injuries of the oesophagus. S. Afr. M. J., 1955, 29: 195–205.

9. Idem. Caustic strictures of the oesophagus. Thorax, Lond., 1955, 10: 171–181.
10. Merendino, K. A., and Emerson, E. C. Aorto-esophagogastric fistula, unusual complication of esophagogastrostomy performed under aortic arch following esophageal resection for carcinoma; report of 2 cases. J. Thorac. Surg., 1950, 19: 405–411.
11. Nuboer, J. F. Remarques sur la vagotomie dans le traitement chirurgical des ulceres gastroduodénaux. Acta gastroenter. belg., 1949, 12: 380–384.
12. Orr, I. M., and Johnson, H. D. Vagotomy for peptic ulcer; indications and results. Brit. M. J., 1949, 2: 1316–1319.
13. Sweet, R. H. Surgical management of carcinoma of midthoracic esophagus; preliminary report. N. England J. M., 1945, 233: 1–7.
14. Tanner, N. C. Med. Ann., 1951, p. 205.
15. Tucker, G. Strictures of the esophagus; their diagnosis and treatment. Laryngoscope, 1931, 41: 426–439.
16. Vinson, P. P. Cicatricial (benign) stricture of esophagus; tabulated report of 186 cases. Ann. Otol. Rhinol., 1927, 36: 40–56.
17. Yudin, Serge S. The surgical construction of 80 cases of artificial esophagus. Surg. Gyn. Obst., 1944, 78: 561–583.

OSTEOMYELITIS OF THE VERTEBRAE AS THE RESULT OF INFECTION OF THE URINARY TRACT

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A BETTER UNDERSTANDING of osteomyelitis of the spinal column has made the diagnosis and treatment of this condition more satisfactory than in the past. New procedures permit earlier diagnosis and specific drug therapy prevents disabling complications. Certain unusual features of the disease, however, tend to delay the diagnosis; and, because mild forms exist that have an insidious onset, run a mild course, and may even heal spontaneously, it seems pertinent to review the clinical syndrome and to stress the diagnostic procedures that may save months and even years of pain and disability.

INCIDENCE

The incidence of osteomyelitis of the vertebrae was reported by Hahn in 1895 as 1 in 661 cases of osteomyelitis, by Wilensky in 1929 as 9 in 578 cases, and by Kulowski in 1936 as 60 in 1,500 cases. Thus in 0.2, 1.6, and 4.0 per cent, respectively, of all cases in these series osteomyelitis occurred in some portion of the spinal column. It is probable that the disease is commoner than these figures tend to indicate and that in many cases obscure pain in the back is explained on the basis of low grade infection that smolders for years before spontaneous healing or frank suppuration occurs.

Earlier reports indicated a peak incidence during adolescence in common with other forms of osteomyelitis, but recent series have given an average age in the fourth decade of life. The reasons for this increase in age are not readily apparent. It may be that improved diagnostic procedures have resulted in more frequent detection of mild cases in an age group whose natural resistance is higher, and, therefore, the disease is less serious and fewer complications develop. It is interesting that in Makins and Abbott's series in 1896 the average age was 14 years. All patients had serious complications and the mortality rate was 71 per cent. Contrasting sharply with these data are those of Kulowski in 1936. The average age of his patients was 31 years; serious complications were much less frequent and the mortality rate was 25 per cent. In the large series of reported cases the ratio of male patients to female patients was about 3:1.

The distribution of the lesions in the spinal column shows a consistent predilection for the lumbar region, followed in frequency by lesions in the dorsal and cervical regions. Four of our 7 patients had infections in the lumbar portion of the spinal column, 2 in the thoracic portion, and 1 in the dorsolumbar portion. Table I shows the distribution in five large series of cases covering a 56 year period. Of the total lesions, 54.6 per cent occurred in the lumbar region, 25.9 per cent in the dorsal region, and 10.3 per cent in the cervical region.

PATHOGENESIS

Osteomyelitis of the vertebrae is hematogenous in most cases, but may occur directly from penetrating wounds or extension from adjacent infection. Bacteremia may follow an infection on any surface of the body, including the mucous membranes, and the organisms may enter the blood as a result of trauma, or when they come in

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TABLE I.—DISTRIBUTION OF LESIONS IN OSTEOMYELITIS OF THE VERTEBRAE

	Makins and Abbott (12) 1896	*Wilensky (17) 1929*	*Klein (9) 1933*	*Kulowski (10) 1936*	*Wear (16) 1952*	*Total*	*Per cent*
Lumbar	10	4	13	51	23	101	54.6
Dorsal	5	2	3	31	7	48	25.9
Cervical	3	2	3	8	3	19	10.3
Sacral	3	1	1	9	—	14	7.6
Coccyx	—	—	—	3	—	3	1.6
Totals	21	9	20	102	33	185	100.0

contact at some point with the circulating blood.

The urinary tract as a source of infection has received considerable attention in the past, but its special role in osteomyelitis of the vertebrae has not been fully appreciated. In 1931 Carson reported the cases of 4 patients having osteomyelitis of the vertebrae, all of whom had infections of the urinary tract and cultures of blood which were positive for Staphylococcus aureus. He considered the source of infection to be a boil in 3 cases and a subcutaneous abscess in the fourth. He made no attempt to explain the association of the urinary tract and vertebral lesions. In 1934 Selig reported a case of metastatic osteomyelitis, involving two cervical vertebrae, that occurred during the course of bacteremia caused by Proteus after cystoscopy. Kusunoki in 1938 was able to find reports of only 6 cases of osteomyelitis complicating infections of the urinary tract; in 3 cases osteomyelitis occurred in the vertebrae. He added a case of osteomyelitis of the vertebrae caused by Pseudomonas pyocyaneus which followed dilatations for a urethral stricture. Deming and Zaff, in 1942, reported 3 cases of acute metastatic vertebral osteomyelitis complicating prostatic operations; they suggested a definite etiologic relationship between infection of the urinary tract and the lesion in the spine. They considered the portal of entry to be the prostatic urethral veins which connect with the vertebral veins.

The role of the vertebral veins in metastatic processes was demonstrated by Batson when he showed that the vertebral veins could be filled by injecting radiopaque material into the dorsal vein of the penis. The distribution of metastatic infections in the spinal column, with more than half of the lesions occurring in the lumbar region and a decreasing incidence in the thoracic and cervical regions, is exactly what one would expect if showers of organisms were intermittently released into the vertebral veins from the lower urinary tract. Furthermore, when the offending organism proves to be one commonly found in the urinary system, such as Escherichia coli, Proteus, or Pseudomonas, and if there is a history of previous or intermittent pyuria, it is likely that the urinary system is the primary source of infection. When the primary focus appears to be a pyodermic infection, such as in the cases reported by Carson, it is possible that the vertebral infection resulted from secondary involvement of the urinary system by pyoderma. The usual late appearance of symptoms involving the back is consistent with this view.

Among patients who have undergone operation the time relationship between the operation and the onset of pain in the back leaves little doubt that the spinal lesion is related to the urinary tract infection. Many patients notice the pain within a few days after operation; it gets progressively worse until a destructive lesion is demonstrated on x-ray examination. A recent report by Chrichton and Hamman illustrates this relationship. A 59 year old man experienced chills and fever 10 days after prostatectomy and severe pain in his back 5 days later. The symptoms continued for 6 months before he was found to have an abscess formation involving the seventh, eighth, and ninth thoracic vertebrae. A blood culture revealed Salmonella typhosa and the response to treatment with chloramphenicol was dramatic.

The patient's wife had had typhoid fever 22 years previously, and the patient himself had never been immunized. The authors concluded that a focus of infection in the prostate, dormant for 22 years, had been activated by the operation, resulting in bacteremia and the spinal lesion.

That metastatic infection from the urinary tract can occur without instrumentation or manipulation is indicated by the fact that 3 of our patients (Cases 1, 2, and 6) had no manipulation of any sort prior to the development of bacteremia and subsequent osteomyelitis of the vertebrae.

A wide variety of causative organisms have been reported in osteomyelitis affecting the vertebrae. As Bickel has emphasized, Table II shows the relative frequency as reported in three large series. Among our patients is 1 in whom the infection was caused by Alcaligenes faecalis, (Case 5) proved by needle biopsy. To our knowledge this organism has not been reported previously as a cause of osteomyelitis involving the vertebrae.

Four important phases are recognized in the pathogenesis of osteomyelitis of the vertebrae. The first is a focus of infection, often in the urinary tract; the second is the period of bacteremia which may or may not be symptomatic; the third is localization of the infection in the vertebrae; the fourth is the stage of extension or complication.

TABLE II.—ORGANISMS RESPONSIBLE FOR OSTEOMYELITIS OF THE VERTEBRAE

Organism	*Klein (9) 1933*	*Kulowski (10) 1936*	*Guri (7) 1946*	*Total*	*Per cent*
Staphylococcus	7	55	15	77	72
Streptococcus	3	10	3	16	15
Pneumococcus	3	—	—	3	2.8
Pyocyaneus	1	—	—	1	0.9
Friedländers bacillus	1	—	—	1	0.9
Proteus	1	—	—	1	0.9
Mixed	—	8	—	8	7.5
Total	16	73	18	107	100.0

SYMPTOMS

The onset of osteomyelitis of the vertebrae may be abrupt and the course fulminating, or the onset may be insidious and the course slowly progressive. Spontaneous recovery, undoubtedly, occurs in many mild cases. Bacteremia, in the acute forms, is characterized by chills, fever, and varying degrees of prostration. In the more chronic forms bacteremia is frequently absent or not appreciated by the patient or his physician. Many times the patient has received transient antibiotic therapy for what was termed a cold or the flu; this treatment modifies the further course of the disease.

Localization of the disease in the vertebrae follows the bacteremia by periods varying from a few days to months or years. Pain and rigidity are the most constant symptoms. Tenderness is usually present over the involved region. Anorexia and malaise are prominent symptoms and loss of weight may be severe. The pain is usually constant, of gradually increasing severity and aggravated by any motion of the vertebrae. It is worse when standing and incompletely relieved by rest in bed and external heat. It is frequently more noticeable at night. Extension of the pain may suggest intrathoracic or intra-abdominal disease, and sciatic pain may simulate the pain of a protruded intervertebral disc with typical aggravation on coughing and sneezing. Roentgenograms of the spinal column taken at this time are likely to be without evidence of abnormality, but others should be made periodically.

Complications are due to extension of the disease. Local abscess formation is the commonest complication, and the manifestations depend on the location of the lesion in the vertebrae and the distribution of the abscess in the spinal column. In rare cases the abscess may be subcutaneous, but more commonly collections of pus form and spread along the longitudinal ligaments and the fascial planes. The abscess may point a considerable distance from the involved vertebrae. The most serious complication is extension into the spinal canal with suppurative meningitis or paraplegia from extradural compression. Other complications include extension to other vertebrae, metastatic abscesses to distant sites, and death.

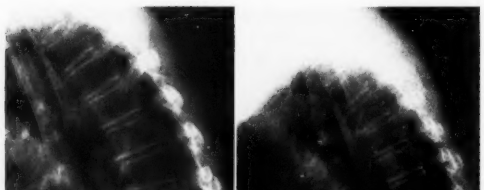

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FIG. 1. Case 1. Lateral views showing osteomyelitic involvement of eighth, ninth, and tenth thoracic vertebrae. a, At time of diagnosis. b, Solid bony union in 8 months.

ROENTGENOGRAPHIC FEATURES

A satisfactory roentgenogram is one of the most important factors in making the diagnosis. Adequate preparation of the patient with castor oil and enemas is essential so that finer trabecular details are not obscured by gas and feces. Three-quarter, anteroposterior, and lateral views localized over the point of maximal pain frequently are necessary. It is not unusual for such special views to show evidence of the lesion after routine films have failed to do so. Repeated studies are essential both in making the diagnosis and in following the course of the disease. Pain and rigidity may be present for months before a lesion is demonstrable roentgenographically. Similarly, pyogenic lesions in the early stages may be indistinguishable from tuberculous lesions, and it is only after serial roentgenograms are taken that the more rapid course of pyogenic infection is appreciated.

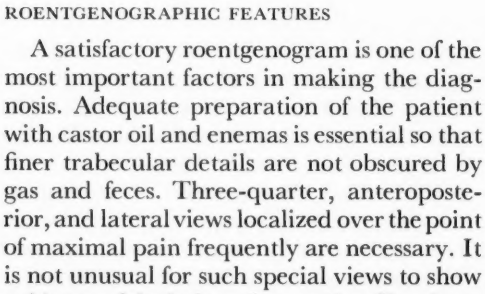

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FIG. 2. Case 3. Infection of superior border of fourth lumbar vertebrae and adjacent disc. a, Lateral view. b, Biopsy needle in place.

The earliest bony changes, as seen by roentgenograms, are rarefaction and loss of trabecular detail. As destruction progresses it most frequently appears as a fuzziness along the upper or lower bony plates. Partial or complete collapse of the vertebrae with angulation may occur. Early and rapid narrowing of the intervertebral disc develops as the infection extends to involve this structure, or when the disc protrudes into the diseased vertebra. Narrowing of the disc often is the earliest sign of infection and may precede any demonstrable involvement of bone. Changes in the soft tissue include paravertebral abscesses and those which may obscure or displace adjacent structures. As attempted healing takes place reactive new-bone formation appears, manifested by increasing sclerosis and eventually by bony bridging anteriorly and laterally. It is this latter feature, together with the rapid progress of the lesion, that helps to distinguish pyogenic lesions from tuberculosis.

DIAGNOSIS

The clinical features in a typical case of osteomyelitis of the vertebrae should strongly suggest the diagnosis. A bacterial infection, followed by a febrile episode, and the subsequent development of localized pain and rigidity of the spinal column are characteristic. When adjacent structures are involved or radiating pains are prominent, atypical clinical syndromes result which are described as abdominal pain, chest pain, sciatic pain, and meningeal irritation.

Laboratory studies usually are inconclusive. Leucocytosis may occur in the acute phase; anemia is common in chronic cases and may be advanced. The sedimentation

rate of erythrocytes is rather consistently elevated in our experience, and in the acute phase it is usually more than 100 millimeters in the first hour (Westergren method).

If an infectious lesion is suspected a search should be made for the primary focus which may be on the skin or in the urinary tract, the lungs, or the gastrointestinal tract. Cultures of blood, urine, sputum, or other suspected material should be made in an effort to isolate the organism.

When the roentgenograms permit accurate localization of the lesion, needle biopsy can be performed with recovery of material for culture and sensitivity studies. This allows an accurate bacteriologic diagnosis to be made and specific therapy to be carried out. This procedure was first reported by Ball in 1934 and the technique described in detail by Valls and associates in 1948. Various modifications of Valls' technique have been described. Fluid can be aspirated or plugs of bone and tissue removed with a serrated biopsy needle such as the one described by Turkel and Bethell, and by Craig. Occasionally, open biopsy or a combination of open biopsy and needle biopsy is more satisfactory.

Getting the right material for study requires accurate placement of the needle, and this is best accomplished under x-ray control. The approach may be made laterally through the skin and muscles of the back or the back may be opened and the needle placed under direct vision. When the roentgenogram shows that the needle is in the lesion, tissue can be removed for frozen sections. These sections are of value in identifying the tissue, but histologic appearance is often misleading and final diagnosis must await cultures. In the absence of a positive bacteriologic diagnosis based on biopsy of the lesion, a presumptive diagnosis may be made based on evidence supplied by skin tests, agglutination studies, roentgenographic features, clinical course, and therapeutic response.

The differential diagnosis, in addition to the common pyogenic infections, includes tuberculosis, brucellosis, fungi, and salmonella infections. Myeloma, metastatic carcinoma, and other malignant lesions must be ruled out. If a roentgenogram of the affected region does not show evidence of a lesion, occasionally the problem arises of ruling out an "acute abdomen" intrathoracic disease, protrusion of an intervertebral disc, or involve-

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FIG. 3. Case 4. a, Infection of the second lumbar vertebra and some narrowing of the disc; lateral view. b, Same view 11 months later showing subsequent involvement of the third lumbar vertebra. Note sclerosis and other evidence of healing.

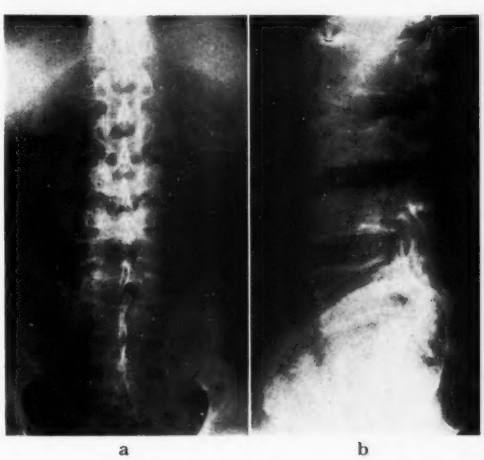

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FIG. 4. Case 5. Osteomyelitic involvement of the second and third lumbar vertebrae and adjacent disc. a, Anteroposterior view. b, Lateral view.

TABLE III.—PERTINENT DATA ON 7 PATIENTS WITH OSTEOMYELITIS OF THE SPINAL COLUMN AND INFECTIONS OF THE URINARY TRACT

Case No. Age, yrs. Sex	History	Symptoms	Pertinent laboratory data	Urinary tract, pathologic condition	X-ray location of lesion	Positive cultures	Results of treatment
1 79 F	Increasing dysuria 7 da., then sudden onset chills, fever 103°F., suprapubic and right renal tenderness; 3 wk. later pain in upper abdomen and back	Pain, rigidity and tenderness over dorsal vertebrae	E. S. R.—20 mm./hr.; pyuria, microhematuria	Duplication right renal pelvis and ureter	Partial collapse T-8, T-9, T-10; pedicles and discs involved	Urine, E. coli; blood, E. coli. Needle biopsy refused by patient	No specific therapy. No pain or tenderness after 4 mos.; solid bony union in 8 mos.
2 69 F	Dysuria followed by chill, fever 103°F.; interscapular pain extending to left part of thorax of increasing severity 5 mos. Treated with penicillin, hyperextension, and cortisone	Pain; rigidity; percussion tenderness of dorsal vertebrae, weakness, numbness, muscle wasting, impaired position sense of lower extremities, unable to stand	E. S. R.—60 mm./hr.; pyuria, microhematuria	Passed innumerable "kidney stones" last 15 yr.	Destructive lesion at T-4 and T-5, involvement of pedicle at T-5	Urine, E. coli	No specific therapy. Bony union without pain in 9 mos.; mobilized on crutches with residual lower-motor neuron damage
3 40 F	For 4 mos. increasing pain low in back extending into abdomen, worse with motion. Treated with "pain pills," shots, and cortisone. Bedfast 5 wk.	Temperature 100° to 102°F.; pain, rigidity, tenderness over L-5 and S1-2; much dermatitis from heat and 2 inch burn over sacrum	E. S. R.—115 mm./hr.; mild pyuria, microhematuria	None demonstrated	Minimal destruction of superior bony end-plate L-4	Tissue from L-4 grew M. pyogenes, sensitive to penicillin	Afebrile in 4 da.; asymptomatic with corset in 3 wk.; bony union in 3 mos.
4 42 M	Dysuria 1 wk., then chills, fever 104°–105°F. Treated with sulfonamides. Onset of pain in left sternoclavicular joint 10 da. later; pain low in back of increasing severity for 6 wk.; bedfast, 4 wk.; lost 40 lb.	Chronically ill; left sternoclavicular joint red, hot, swollen, tender; pain, rigid back, tenderness in lumbar region. Muscle guarding in left upper quadrant	E. S. R.—110 mm./hr.; pyuria, microhematuria	Gonorrhea at 19 yr. of age; acute urinary retention 10 mo. previous to registration; cystoscopy, catheterization; stricture	Osteolytic process, anterior portion of L-2; no abnormality evident in sternoclavicular joint	Urine, Micrococcus (species?); pus from L. sternoclavicular joint grew M. pyogenes sensitive to erythromycin	Pain in sternoclavicular joint decreased in 5 da. after starting antibiotics; no pain in back after 12 da.; bony bridging in 2 mos.
5 70 M	Transabdominal ureterolithotomy 4 mos. before registration, then pain low in back and in right sciatic region aggravated by coughing and sneezing. Unable to stand because of pain; 5 transfusions since operation, bedfast, 4 mos.	Pain; rigidity; percussion pain in lumbar region; straight-leg raising limited 50 per cent on left; weakness, muscle wasting of lower extremities	E. S. R.—110 mm./hr.; urea, 86 mgm. per 100 c.c. blood	Gonorrhea as youth; renal colic for 5 yr.; right nephrectomy 3 yr. previously; left ureterolithotomy, 4 mos. before	Destruction of fourth disc and contiguous margin of L-3 and L-4	Urine, Aerobacter aerogenes; fluid from fourth disc grew Alcaligenes faecalis sensitive to terramycin	Out of bed with Taylor brace in 2 wk.; no pain in back, minimal in hip and leg; bony fusion in 5 mos.
6 51 M	Strained back lifting, then febrile illness for 2 wk. Treated with penicillin for short period and 4 chiropractic adjustments. Pain in back worse; bedfast 3 wk.; lost 31 lb.	Pain; rigidity; tenderness over L-3-4-5; right thigh painful on flexion; tenderness over ischial tuberosity and sciatic notch	E. S. R.—103 mm./hr.; pyuria, microhematuria	Acute urinary retention 5 mos. before registration with spontaneous relief after 15 hr. (no manipulation); ureteral stricture	Narrowed fourth interspace	Urine, E. coli; pus from fourth disc L-4, L-5 grew E. coli sensitive to terramycin	Bony bridging at L-4-5 in 2 mos.; returned to work in 3 mos.
7 50 M	Sudden onset of pain low in back and in right hip 3 mos. before; increasingly severe; difficulty in walking, bending, getting up from chair. Treated with narcotics and cortisone; x-ray to back without relief	Pain; marked limitation of movements in all directions; temperature, 100.2° F.	E. S. R.—105 mm./hr.; pyuria, microhematuria; hemoglobin, 9.6 gm. per 100 c.c. blood	Passed kidney stone 10 yr. previously; cystoscopy for left ureterolithiasis 7 mos. before	Destruction of T-11-12 and L-1-2 and adjacent cortices	Pus from L-1 grew Pseudomonas (species?); resistant to streptomycin and terramycin	Solid bony fusion in 6 mo. after immobilization with cast. E.S.R. 18 mm./hr.

ment of the spinal cord or nerve roots or both.

TREATMENT

The following treatment is usually successful if a positive diagnosis has been made: specific antibiotic therapy as determined by culture and sensitivity studies; splinting of the spinal column with a plaster cast, a brace, or a corset, until x-ray evidence of healing is manifested; general supportive measures regarding pain, fluids, and diet; rest in bed until fever has subsided and symptoms have abated, then gradual mobilization; and surgical drainage of abscesses when necessary. When fusion of the involved vertebrae has occurred the disease is usually cured and will remain so.

REPORT OF CASES

These cases, encountered at the Mayo Clinic, illustrate the importance of the urinary tract as a source of infection (Table III; Figs. 1 to 4). Four patients (Cases 1, 2, 4, and 6) had acute febrile illnesses; the fever followed a period of dysuria in 3 cases and in 1 case it started immediately after the patient had strained his back. Pathologic conditions of the urinary tract included renal lithiasis in 3 cases, urethral strictures in 2, and duplication of the renal pelvis and ureter in 1 case. Of the patients who had had urethral manipulation, 2 had had cystoscopy and 1 had had urethrolithotomy. Four patients had not had urethral manipulation, but 1 of these was found to have a stricture and 1 had a history of renal stones.

In 5 cases the diagnosis was confirmed by needle biopsy. One patient refused biopsy and the condition of another patient was diagnosed clinically as a metastatic malignant lesion. The latter patient returned to the clinic in 4 months showing definite improvement; neurologic symptoms had abated; and healing was taking place, as evidenced by beginning bony union of the involved vertebrae. The delay from the onset of back pain until diagnosis varied from 2 to 9 months, with an average of 4 months.

SUMMARY AND CONCLUSIONS

Osteomyelitis of the vertebrae is not as rare as is generally believed, and patients with obscure pain in the back may have a low grade infection that goes unrecognized unless complications occur.

Four important phases are recognized in the pathogenesis of the disease, as follows: precipitating infection, bacteremia, localization in the spinal column, and extension or complication.

Infection of the urinary tract is an important primary focus, and although a surgical procedure or other manipulation is the usual precipitating factor, it is not essential to the development of bacteremia and subsequent osteomyelitis of the vertebrae.

Roentgenographic evidence of infection in the vertebrae is frequently delayed, and serial roentgenograms should be taken if osteomyelitis is suspected. Osteomyelitis should be suspected in all cases of otherwise unexplained pain in the back.

Needle biopsy is a safe and early method of making the diagnosis. At times, open biopsy of the vertebrae or a combination of hemilaminectomy and needle biopsy is more satisfactory. Many months, and even years, of pain and sometimes permanent disability may be avoided by the timely use of such biopsy procedures.

REFERENCES

1. BALL, R. P. Needle (aspiration) biopsy. J. Tennessee M. Ass., 1934, 27: 203–205.
2. BATSON, O. V. The function of the vertebral veins, and their rôle in the spread of metastases. Ann. Surg., 1940, 112: 138–149.
2a. BICKEL, W. H. Infectious lesions of the vertebral column. Proc. Mayo Clin., 1951, 26: 477–480.
3. CARSON, H. W. Acute osteomyelitis of the spine. Brit. J. Surg., 1931, 18: 400–408.
4. CHRICHTON, E. P., and HAMMAN, H. A. Typhoid osteomyelitis of spine treated with chloramphenicol. Canad. M. Ass. J., 1953, 69: 529–530.
5. CRAIG, F. S. "Craig vertebral body biopsy kit." Scientific exhibit at The American Academy of Orthopaedic Surgeons, Los Angeles, January 29 to February 3, 1955.
6. DEMING, C. L., and ZAFF, FRED. Metastatic vertebral osteomyelitis complicating prostatic surgery. Tr. Am. Ass. Genitourin. Surgeons, 1942, 35: 287–305.
7. GURI, J. P. Pyogenic osteomyelitis of the spine; differential diagnosis through clinical and roentgenographic observations. J. Bone Surg., 1946, n.s. 28: 29–39.

8. Hahn, O. Ueber die primaere akute Osteomyelitis der Wirbel. Beitr. klin. Chir., 1895, 14: 263–278.
9. Klein, H. M. Acute osteomyelitis of the vertebrae. Arch. Surg., 1933, 26: 169–195.
10. Kulowski, Jacob. Pyogenic osteomyelitis of the spine; an analysis and discussion of 102 cases. J. Bone Surg., 1936, n.s. 18: 343–364.
11. Kusunoki, T. Ueber einen Fall von Pyocyaneus-Osteomyelitis der Wirbelsaeule, im Anschluss an Pyelonephritis. Zschr. Urol., 1938, 32: 699–701.
12. Makins, G. H., and Abbott, F. C. On acute primary osteomyelitis of the vertebrae. Ann. Surg., 1896, 23: 510–539.
13. Selig, Seth. Bacillus proteus osteomyelitis of the spine. J. Bone Surg., 1934, n.s. 16: 189–192.
14. Turkel, Henry, and Bethell, F. H. Biopsy of bone marrow performed by a new, simple instrument. J. Laborat. Clin. M., 1943, 28: 1246–1251.
15. Valls, J., Ottolenghi, C. E., and Schajowicz, F. Aspiration biopsy in diagnosis of lesions of vertebral bodies. J. Am. M. Ass., 1948, 136: 376–382.
16. Wear, J. E., Baylin, G. J., and Martin, T. L. Pyogenic osteomyelitis of the spine. Am. J. Roentg., 1952, 67: 90–94.
17. Wilensky, A. O. Osteomyelitis of the vertebrae. Ann. Surg., 1929, 89: 561–570; 731–747.

AN ANALYSIS OF CYTOLOGIC SCREENING FOR UTERINE CANCER (9,815 CASES)

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THE CONTINUING EFFORT directed toward early detection of cancer by cytologic means must be evaluated and the significance of this effort assessed in terms of the accuracy and frequency with which nonsuspected or asymptomatic cancers are discovered.

In January 1948, cytologic examination of uterine cervical smears was instituted at the University of Nebraska Hospital as a screening procedure. For the most part, these smears were prepared by interns. Smears from private sources were also examined. This is a report of a careful study of these smears and cases.

METHODS AND MATERIALS

Smears from a total of 9,815 patients were screened: 6,441 were obtained from the University Hospital and Clinic from January 1948 through December 1954; 3,374 were derived from private sources from January 1948 through June 1952.

Almost uniformly at least 2 smears from each patient were examined. These were prepared from cervical scrapings obtained by a modified Ayre technique and were stained with routine Papanicolaou stains. During this period of study the supervision of the laboratory has been the responsibility of a single physician. In these 7 years, 4 technicians, none of whom have had previous cytology experience, performed the screening.

The smears were interpreted as negative, suspicious, or positive. They were cytologically classified as squamous cell carcinoma, adenocarcinoma, or undifferentiated carcinoma. The records of all cases from the University in which a suspicious or positive interpretation was given were reviewed. The location of the lesion within the uterus was not considered in the adenocarcinoma and undifferentiated carcinoma groups. Questionnaires were submitted to the private physicians to whom reports of suspicious or positive interpretations were given. All private cases were accounted for. Final diagnosis of malignancy was dependent entirely upon the histologic diagnosis made on a surgically removed tissue specimen and was accomplished shortly after receipt of the cytologic report. Final diagnosis of absence of malignancy was dependent upon a clinical follow-up which included two or all of the following: negative biopsy, negative repeat cytology, and lack of clinical evidence of malignancy. False negatives are reported only in the series from the University Hospital and Clinic and only as related to uterine cervical lesions. The false negative cases were tabulated by a review of all diagnoses of squamous cell carcinoma of the uterine cervix made by our department of pathology and a review of our tumor registry.

The records of all patients having nonsuspected carcinoma were carefully checked regarding signs, symptoms, and League of Nations classification of the stage of disease.

RESULTS

One hundred and forty-nine cases were interpreted cytologically as positive (Table I). From this group, 133 were histologically graded as squamous cell carcinoma. Three

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TABLE I

	No. of cases	*Proved cases*	*Pelvic but extrauterine cancer*	*Lost to follow-up*	*Falsely pos. and falsely susp.*	*Falsely neg.*
Squamous cell carcinoma						
Positive	149	133	1	3	12 (7.1%)	4 (3.9%)*
Suspicious	146	46		32	68 (46.5%)	
Adenocarcinoma						
Positive	27	21	2	1	3	
Suspicious	36	7		7	22	
Undifferentiated carcinoma						
Positive	20	15	2	2	1	
Suspicious	25	10		6	9	

*From University services only; 4 of 102 cases (3.9%): 2 cases showed no malignant cells on smears, 1 case had many malignant cells, 1 case resulted from clerical error.

TABLE II.—NONSUSPECTED CASES

	Nonsusp. cases	*Bleeding or spotting contact bleeding or suspicious lesion*	*Heavy discharge or erosion*	*No signs or symptoms*	*Stages*			*Recurrent lesion*
					0	*I*	*II*	
University—6,441 cases	25	8	7	10	5	17	2	1
Private—3,374	8	4		4	5	3		
Total—9,815	33	12	7	14	10	20	2	1

cases were lost to follow-up, 12 (7.1 per cent) were cytologically falsely positive and 1 was a case of extrauterine cancer. One hundred eight of the cytologically positive cases were obtained from the University: 98 of this group were proved correct by biopsy; 3 cases were lost to follow-up; 6 cases were cytologically falsely positive; and 1 case was from extrauterine origin.

In addition, there were 4 cytologically falsely negative reports, giving a total of 102 histologically proved cases of squamous cell carcinoma of the uterine cervix. On reviewing the smears from these 4 cytologically falsely negative cases, 2 cases (1.9 per cent) failed to show malignant cells, 1 case was reported as falsely negative because of a clerical error, and the remaining case showed large numbers of malignant cells. This last falsely negative case was a result of "human error." One hundred and forty-six cases were reported as suspicious for cancer: 46 of these were subsequently proved to be squamous cell carcinoma, 32 cases were lost to follow-up, and 68 (46.5 per cent) cases proved to be cytologically falsely suspicious.

From 257 University cases with a positive or suspicious interpretation, 137 were proved to have squamous cell carcinoma (Table II). Twenty-five of these cases were not suspected clinically. On review of the charts of these patients, 8 were found to have a history of bleeding or spotting, contact bleeding, or a lesion grossly consistent with a diagnosis of cancer. Of the remaining 17 patients, 7 had a heavy discharge or an erosion; 10 had neither signs nor symptoms.

Of this group of 25, 1 represented a recurrent lesion 2 years following cervical amputation for carcinoma; 5 were stage 0 (without evidence of stromal invasion); 17, stage I; and 2, stage II.

From the private patients, a total of 77 cases were interpreted cytologically as suspicious or positive. Forty-two were proved to have squamous cell carcinoma of the cervix. Eight of these cases were not suspected clinically; 4 had neither signs nor symptoms, while 4 had a history of bleeding or contact bleeding on examination.

Smears interpreted as positive for adenocarcinoma totaled 27. In 21 cases there was histologic evidence of adenocarcinoma, 3 were cytologically falsely positive, and 2 were of extrauterine origin. Thirty-six cases were reported as suspicious. Of these, 7 had histologic evidence of adenocarcinoma, 7 cases were lost, and 22 were falsely suspicious. Twenty cases were reported as positive for undifferentiated carcinoma. Fifteen were histologically proved as malignant from the

uterus. Two were from extrauterine origin, 2 were false positive, and 1 case was lost. Twenty-five cases were reported as suspicious for undifferentiated carcinoma. Of these, 10 were histologically proved malignant, 6 were falsely suspicious, and 9 cases were lost to follow-up.

COMMENTS

Various authors report a considerable variation in incidence of cancer of the uterus as detected by the cytologic method. Graham's selected group has a high incidence, 50 per 1,000, whereas, Kimmelstiel and associates report only 5.7 per 1,000. Based on the size of the reported series, the most impressive report is that of Erickson and Dunn who show an incidence of 8.2 per 1,000 in 60,000 cases. Our incidence is about 23 per 1,000.

Lack of uniformity in terminology in reporting cytologic smears makes comparative evaluation of different series difficult. The accuracy of this laboratory based on positive histologic diagnoses is as follows:

Falsely positive, 7.1 per cent; falsely suspicious, 46.5 per cent; and falsely negative 3.9 per cent (corrected falsely negative 1.9 per cent[1]). Excluding our falsely suspicious group, accuracy is comparable to that of Erickson and Dunn who report 5.5 per cent falsely positive and 3.2 per cent falsely negative.

This screening procedure has led to the diagnosis of 33 cases of nonsuspected carcinoma of the cervix. Although our incidence of nonsuspected cancers of the cervix is lower than the reports of others, it appears that it should be further reduced. In 12 of these cases there were classic signs or symptoms which were not recognized as significant until after receipt of the cytologic report. In 14 there were neither signs or symptoms. These cases plus those with nonspecific signs or symptoms total 21. Significantly, only 10 were stage 0, while 20 were stage I, and 2 were stage II. One represented a recurrence.

[1]Representing smears without malignant cells.

SUMMARY

1. Uterine cervical smears from 9,815 cases were screened.

2. Four hundred and three positive and suspicious smears represented 233 uterine cancers.

3. From the smears of uterine cervical lesions, of those cytologically positive, 7.1 per cent were falsely positive and 3.9 per cent of the histologically positive cases were falsely negative.

4. Thirty-three cases of nonsuspected uterine cervical cancer were discovered.

5. Seventeen patients not suspected clinically of having cervical cancer lacked classic signs or symptoms, and detection would not have been accomplished without cytologic study.

6. From the 33 nonsuspected lesions, 10 were League of Nations stage 0, 20 were stage I, and 2 were stage II. One was a recurrence.

REFERENCES

1. ERICKSON, C. C., and DUNN, J. E. The cytologic technique in the Memphis Shelby County (Tennessee) population uterine cancer screening project; report on first 60,000 women examined. Vaginal Cytology Exhibit, American Medical Association Meeting, June 1955.
2. GRAHAM, RUTH. The value of cytology in the diagnosis of cancer of the cervix. National Cancer Conference, 1952, 2: 1224–1237.
3. KIMMELSTIEL, P., PIXLEY, R. K., and CRAWFORD, J. A statistical review of 22,000 cases examined by cervical smears. North Carolina M. J., 1954, 15: 538–544.

THE USE OF INTRAVENOUS CHOLANGIOCHOLECYSTOGRAPHY IN THE DIAGNOSIS OF ACUTE CONDITIONS OF THE ABDOMEN

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CHOLECYSTOGRAPHY was introduced as a new diagnostic procedure by Graham and Cole in 1924 (1). In their preliminary report, the intravenous administration of calcium tetrabromophenolphthalein was recommended as the opacifying agent of choice. In rapid succession, sodium tetrabromophenolphthalein, sodium tetraiodophenolphthalein and its isomer sodium phenoltetraiodophthalein superseded, and the prediction was made that substances more satisfactory for visualizing the gallbladder, and even the bile ducts, would be discovered (2). Despite undesirable side effects associated with their intravenous and oral administration, the tetrahalogenphenolphthaleins remained the cholecystographic agents of choice until replacement by oral administration of priodax (iodoalphionic acid) in 1940, and more recently by telepaque (iodopanoic acid) and teridax (tri-iodoethionic acid). Priodax and telepaque have proved effective cholecystographic agents because of minimal toxicity and ability to cast a dense homogenous shadow. Even with the utilization of these improved bile contrast media, unpredictable factors related to their absorption from the gastrointestinal tract have made it frequently difficult to evaluate faint or absent gallbladder shadows. Roentgenograms of the extrahepatic bile ducts can be obtained but with insufficient regularity and clarity to make these substances diagnostically useful, particularly with patients who have undergone cholecystectomy.

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In 1953 the introduction of biligrafin, known as cholografin in the United States, provided an intravenous bile contrast agent of low toxicity that eliminated the uncertainty of gastrointestinal absorption and was sufficiently dense to visualize the extrahepatic bile ducts with regularity even when the gallbladder was absent. The ability of cholografin to provide a nonoperative cholangiogram was quickly recognized in several reports. It has not been emphasized, however, that the high iodine content of cholografin, which makes it particularly suitable for cholangiography, also makes it unsuitable for routine cholecystography. The latter examination is primarily a function test which requires concentration of the contrast medium in the gallbladder before visualization can be obtained. It is impossible to evaluate this function with cholografin since its density makes concentration unnecessary to produce opacity.

Although cholografin is not a panacea for cholangiocholecystography, it provides a new approach to the anatomy, pathology, and physiology of the extrahepatic biliary system. Its primary application has been in the field of nonoperative cholangiography. It has also been suggested for diagnosis of tumor in the porta hepatis, for evaluation of hepatic function, and for diagnosis of cases in which oral technique is not feasible. As yet, little attention has been focused on the role cholografin may serve in the differential diagnosis of acute conditions of the abdomen when acute cholecystitis is a consideration.

The primary aim of this study is to evaluate cholografin with special reference to this diagnostic problem. Its value for this

purpose is predicated on the assumption that cystic duct obstruction associated with acute cholecystitis would prevent visualization of the gallbladder. The majority of the 56 cases studied exemplified this problem. The remaining nonacute cases provided data for a comparison of intravenous and oral cholecystography and for evaluation of cholografin for nonoperative cholangiography.

MATERIALS AND METHODS

Cholografin. Cholografin is a 20 per cent isotonic solution of the disodium salt of N,N adipyl-bis (3-amino-2, 4, 6-triiodo) - benzoic acid whose empiric formula is $C_{20}H_{12}O_6N_2I_6Na_2$. This substance is a crystalline powder which becomes a colorless solution when dissolved in water. Its molecular weight is 1183.35 and its iodine content is 64.32 per cent. The iodine atoms are firmly bound to the molecule and remain attached after intravenous injection. Normal subjects excrete 90 per cent of the compound by the liver and 10 per cent by the kidneys. In patients with abnormal hepatic function, less of the dye is excreted by this organ and an increasing amount is excreted by the kidneys. When cholografin reaches the gastrointestinal tract in the bile it does not re-enter the enterohepatic circulation. The toxicity of cholografin is low; the medial lethal intravenous dose for rats has been reported as 3.4 grams per kilogram of body weight.

Patients studied. Administrations were completed 66 times in 56 patients. These patients ranged in age from 26 to 80 years; all were males except for 3 females. Thirty-four patients were admitted for acute conditions of the abdomen suggestive of acute cholecystitis. Cholografin examinations were performed to establish the validity of this diagnosis. In 22 patients a comparative study of oral and intravenous methods of cholecystography was made. Nine of these patients were also studied for possible common duct calculi after cholecystectomy.

Preparation prior to radiographic study varied with the intent of the examination.

TABLE I.—USE OF CHOLOGRAFIN IN PATIENTS WITH ACUTE ABDOMINAL CONDITIONS

Diagnosis	*No. of patients*
Acute cholecystitis	17
Acute pancreatitis	7
Acute cholecystitis and pancreatitis	2
Diverticulitis of colon	2
Perforated duodenal ulcer	1
Posterior penetrating duodenal ulcer	1
Pyloric obstruction	1
Small bowel obstruction	1
Gastroenteritis	1
Narcotic withdrawal	1
Total	34

All patients were tested for sensitivity with 1 cubic centimeter of intravenous cholografin, unless an allergic history existed. Such patients were tested intradermally with 0.1 cubic centimeter of cholografin. The standard dose for those showing no reactions to these tests was 40 cubic centimeters injected over a 7 to 10 minute period. Patients with acute abdominal conditions received no further preparation since they were unable to withstand enemas, purgatives, and dehydration. All other patients received castor oil the night before examination, and cleansing enemas the next morning. Breakfast and lunch were withheld prior to roentgenographic study.

Roentgenographic technique. The roentgen factors employed were 400 milliampere seconds and, depending on the size of the individual, 40 to 60 kilovolts. Patients were placed in the left anterior oblique position with the roentgen tube centered over the gallbladder area at a distance of 36 to 40 centimeters from the table top. The Potter-Buckey diaphragm and a small cone were used to increase contrast and to reduce stray irradiation. Position and exposure factors were checked by preliminary roentgenograms. Subsequently, serial roentgenograms were made on 8 by 10 inch films at 10, 15, 20, 25, 30, 60, and 90 minutes following injection.

Laboratory values. The maximum normal value for bromosulphalein (BSP) retention 45 minutes after injection (5 milligrams per kilogram) was 6.5 milligrams per cent. Other normal blood chemistry values were: total serum bilirubin 0.3 to 1.5 milligrams per

TABLE II.—DEGREE OF VISUALIZATION OBTAINED WITH CHOLOGRAFIN IN PATIENTS WITH ACUTE ABDOMINAL CONDITIONS

	No. of cases		
Diagnosis	*Common duct and gallbladder*	*Common duct*	*No visualization*
Acute cholecystitis....	1	7	9
Acute pancreatitis....	3	0	4
Acute cholecystitis and pancreatitis.....	0	0	1
Other conditions.....	8	0	0

cent; alkaline phosphatase 4.0 Shinawara units; thymol turbidity 0 to 4.0 units; serum amylase 60 to 150 units per 100 cubic centimeters.

RESULTS

Reactions. Examination of the extrahepatic biliary system was contemplated 68 times in 58 patients. Two patients were eliminated from study because of their responses to the sensitivity test. The first, who previously had a reaction following intravenous pyelography, received an intradermal injection of 0.03 cubic centimeter of cholografin. Within 10 minutes, he developed sweating, dizziness, nausea, vomiting, and severe dyspnea which required benadryl and epinephrine. The second patient developed a large erythematous wheel with bullae after intradermal injection of 0.1 cubic centimeter of cholografin. Examinations were performed 66 times in the remaining 56 patients. All patients except 2 received 40 cubic centimeters of dye. An infusion accidentally made into the brachial artery in 1 patient was terminated without complication after 15 cubic centimeters because of pain in the arm. Injection was discontinued in a second patient after 25 cubic centimeters because of hypotension. Visualizations of portions of the biliary systems were obtained in both instances but were unsatisfactory for interpretation. The results of this study, therefore, are based on 64 injections in 54 patients.

Reactions associated with intravenous cholografin consisted of urticaria 1, nausea and vomiting 2, hypotension 1, and chill 2. The only serious reaction occurred in the patient who received 0.03 cubic centimeter of cholografin intradermally. This low rate was due possibly to the fact that the reactions were unrecognized since the majority of patients were acutely ill and already complaining of nausea, vomiting, pain, and dyspnea. No reactions were encountered at the first injection in the 10 patients who received cholografin twice at 4 to 6 week intervals. At the second injection, giant urticaria, which responded promptly to epinephrine, occurred in 1 patient; a shaking chill associated with cyanosis and shortness of breath occurred about 1 hour after injection in another. Administration of oxygen brought prompt recovery.

Cholografin examination in patients with acute abdominal conditions. Patients with abdominal complaints suggestive of acute cholecystitis were subjected to intravenous cholangiocholecystography; 33 received the full complement of cholografin. The final diagnoses are listed in Table I and the types of visualization are listed in Table II. A cholangiogram without a cholecystogram occurred in 7 patients. Diagnosis of acute cholecystitis was verified in each of these patients at time of laparotomy. The common duct and gallbladder were visualized in 12: 1 with acute cholecystitis; 3 with acute pancreatitis; and 8 with other acute abdominal conditions. In the 11 cases without cholecystic disease the diagnosis was confirmed either surgically or by normal cholecystogram after oral priodax. The diagnosis of cholecystic disease was substantiated in the other case by nonvisualization of the gallbladder with priodax after recovery. No visualization of the extrahepatic biliary system occurred in 14 patients. A diagnosis of cholecystitis, pancreatitis, or a combination of both was confirmed by operation in 12. After the acute episodes subsided in the remaining 2 patients, the demonstration with priodax of a normal gallbladder suggested pancreatitis in 1; cholografin visualization of the common duct in the absence of a cholecystogram suggested cholecystitis in the other (Table III).

Evidence of jaundice was absent in 10 of the 14 patients in this latter group. In [illegible] of

TABLE III.—USE OF CHOLOGRAFIN IN PATIENTS WITH ACUTE ABDOMINAL CONDITIONS AND NO VISUALIZATION OF BILIARY SYSTEM IN 14 PATIENTS

Patient	*Diagnosis*	*Diagnosis verified by*	*Per cent, BSP retention*	*Serum bilirubin, mgm. per cent or clinical evidence of jaundice*	*Serum amylase units/100 c.c.*
J.R.	Acute cholecystitis	Surgery	27.0	No jaundice	—
P.T.	Acute cholecystitis	Surgery	19.9	No jaundice	40
E.S.	Acute cholecystitis	Surgery	20.7	0.7	120
R.R.	Acute cholecystitis	Surgery	22.2	1.3	60
A.A.	Acute cholecystitis	Surgery	—	10.0	44
E.U.	Acute cholecystitis	Surgery	—	1.6	44
F.C.	Acute cholecystitis	X-ray	8.6	No jaundice	—
B.B.	Acute cholecystitis	Surgery	18.5	No jaundice	44
E.M.	Acute cholecystitis Acute cholecystitis	Surgery	12.6	2.06	80
L.S.	Acute pancreatitis	Surgery	31.4	No jaundice	1200
J.G.	Acute pancreatitis	Surgery	33.0	3.3	280
H.S.	Acute pancreatitis	X-ray	—	No jaundice	288
R.W.	Acute pancreatitis	Surgery	—	4.8	562
J.K.	Acute pancreatitis	Surgery	45.6	No jaundice	322

these, the BSP retention ranged from 8.6 per cent to 45.6 per cent in 45 minutes. Seven of the 10 patients were re-examined after recovery with either cholografin or priodax (Table IV). Jaundice remained absent and the BSP had returned to normal prior to re-examination in all but 1 patient. He had acute cholecystitis and acute pancreatitis, and was the most severely ill patient in the entire series. Roentgenologic representation of the extrahepatic biliary system was obtained at the second examination in all but this 1 patient whose BSP retention remained elevated at 17.8 per cent.

These acute alterations in BSP retention as well as the absence of cholografin visualization of the extrahepatic biliary system in cases of acute cholecystitis or acute pancreatitis can be correlated positively with the duration and severity of the illness. Visualization of the extrahepatic biliary system occurred with all patients ill for 24 hours or less, but was obtained with only 25 per cent of those ill for a longer period.

Comparison of intravenous and oral cholecystography. A comparative study of intravenous cholografin and oral priodax was made in 22 cases in which the diagnosis of cholecystitis was considered. The results are listed in Table V. Cholecystitis was demonstrated at the time of laparatomy in 4 patients whose cholangiograms were obtained with cholografin and for whom no visualizations were obtained with priodax. The common duct and gallbladder were visualized in 4 cases using cholografin although no visualizations were obtained with priodax. One of these patients had undergone sphincterotomy and another had undergone vagotomy and gastroenterostomy. In each, the altered physiology of the sphincter of Oddi did not allow retention of bile so that the priodax might become sufficiently concentrated to cast a roentgenographic shadow. This result was well demonstrated in the case involving vagotomy and gastroenterostomy (Fig. 1). Cholecystitis existed in the remaining 2 patients. The intravenous technique was of no diagnostic value in these cases but was important in the second case, in which examination was performed during the acute phase of illness, in providing reassurance that perforation of the gallbladder need not be feared as an imminent complication. In 6 cases the absence of visualization of the extrahepatic biliary tree after both methods could be explained by an increase in serum bilirubin or alteration in some other hepatic function. Cholecystic disease was present in 4 of these patients. Cholecystograms were obtained by both methods in the remaining 8 cases in which cholecystic disease was absent.

Use of cholografin for nonoperative cholangiography. Experience with cholografin for this purpose was limited to 9 patients. Cholangiograms were obtained in 7 cases, with calculi visible in 1. Cholangiograms were not

TABLE IV.—CORRELATION BETWEEN BILIARY TRACT VISUALIZATION AND BSP RETENTION IN 7 PATIENTS WHILE ACUTELY ILL AND AFTER RECOVERY

		Initial				Follow up		
Patient	*Diagnosis*	*Per cent, BSP retention*	*Icterus*	*Results with cholografin*	*Days between examinations*	*Per cent, BSP retention*	*Contrast agent*	*Results*
R.R.	Acute cholecystitis	22.2	None	No visualization	14	1.5	Cholografin	Visualization
P.T.	Acute cholecystitis	19.9	None	No visualization	9	4.6	Cholografin	Visualization
E.S.	Acute cholecystitis	20.7	None	No visualization	13	5.1	Priodax	Visualization
T.C.	Acute cholecystitis Acute cholecystitis	8.6	None	No visualization	21	2.0	Cholografin	Visualization No
L.S.	Acute pancreatitis	31.4	None	No visualization	56	17.8	Cholografin	Visualization
J.R.	Acute cholecystitis	27.0	None	No visualization	90	3.0	Cholografin	Visualization
J.K.	Acute pancreatitis	45.6	None	No visualization	13	6.5	Priodax	Visualization

obtained in 2 cases because of abnormal hepatic function. This factor was obvious in 1 patient, J. P., recovering from hepatitis, but less evident in the second, A. D. who was unknown to have any hepatic dysfunction (Table VI).

Correlation of intravenous cholangiocholecystography and hepatic function. The BSP test was performed 30 times in 22 patients and serum bilirubin was measured 20 times in 19 patients. The highest values of BSP retention and serum bilirubin compatible with cholografin visualization of the biliary tree were 14.7 per cent and 3.1 milligrams per cent respectively. Cholografin examination and BSP study were performed in 5 of the cases listed in Table IV during acute illness; BSP was elevated and visualization was absent in each case. After recovery cholografin reexamination resulted in normal visualization in all but 1 case in which the BSP remained elevated. The minimal alteration in hepatic function studies associated with cholografin nonvisualization is exemplified in Table VI.

Radiographic findings. Roentgenographic evidence of cholografin in the extrahepatic biliary system was obtained in 37 cases. The common duct was usually visualized 10 to 15 minutes after injection; the maximum time was 25 minutes. The common duct ranged from 3 to 10 millimeters in patients without cholecystectomy, and 5 to 15 millimeters in patients with cholecystectomy. It was not unusual for the common hepatic duct to measure twice the size of the common duct. Adequate visualization of the terminal portion of the common duct in order to eliminate the possibility of small stones in this area was virtually impossible. Usually evidence of a successful cholecystogram occurred in 10 to 15 minutes and occasionally the opacity at this interval compared favorably to the density obtained at the maximal visualization in 30 to 90 minutes. The degree of gallbladder opacity was unrelated to its ability to concentrate. Fifteen to 20 minutes after injection, the duodenum was outlined to varying degrees in 40 per cent of the cases in which the common duct was visualized. The greatest amounts of dye seen in the duodenum occurred in the 2 patients with altered physiology of the sphincter of Oddi.

TABLE V.—COMPARATIVE STUDY OF CHOLOGRAFIN AND PRIODAX IN PATIENTS NOT ACUTELY ILL

No. of patients studied	*Visualization with cholografin*	*Visualization with priodax*	*No. of patients with cholecystic disease*
4	Common duct	None	4
4	Common duct and gallbladder	None	2
6	None	None	3
8	Common duct and gallbladder	Gallbladder	0

In 15 per cent of cases in which excretion occurred via the liver, a sufficient quantity was excreted also by the kidneys to produce pyelograms. These were usually of poor quality but occasionally excellent even though the excretion of dye into the biliary tree was also adequate. The most pronounced pyelogram, including visualization of the ureters (Fig. 2), occurred with A. C. (Table VI) for whom a cholangiogram could not be obtained. Since evidence of hepatic dysfunction was minimal in this case, a possible ex-

planation for absence of dye in the biliary tree was a low renal threshold rather than abnormal hepatic function. Usually, no difference in clarity was observed between the pyelograms of patients who excreted cholografin by the liver and those who did not. In fact, absence of a pyelogram sometimes occurred in association with an absence of dye in the biliary tree.

DISCUSSION

Cholografin provides the clinician with the means to obtain a cholangiocholecystogram within a 2 hour period. Although this agent constitutes a new approach to the pathology and physiology of the biliary system, certain disadvantages remain. Despite the absence of serious reactions in this study, intravenous administration of a compound with such a high iodine content may be expected eventually to produce serious complications. This disadvantage was suggested by the severe reaction encountered in 1 patient tested intradermally with 0.03 cubic centimeter of cholografin. The high contrast roentgenologic technique to provide sufficient detail for interpretation is safe but must be employed cautiously, since each exposure yields 3 to 4 roentgens to the skin. Our study involved making roentgenograms at specific intervals after injection. Each film was developed before the next exposure to correct the technique or to terminate the examination when the desired information was obtained.

The density of the shadow cast by cholografin in the common duct paralleled the density cast in the gallbladder. Occasionally these were faint and difficult to evaluate. Contrary to other reports correlation of the density of the dye in the gallbladder with its concentrating function was not possible. With more experience this may be possible; however, factors such as hepatic function, pressure within the common duct, and roentgenographic technique have such profound effect upon opacification of the gallbladder and bile ducts that only the presence or absence of these shadows were considered important. Although cholografin is particularly suitable for cholangiography, it cannot be utilized for routine cholecystography. Its density makes concentration by the gallbladder unnecessary to produce visualization, thereby making evaluation of the concentrating function of this organ virtually impossible. Not infrequently, however, the question is raised as to whether a patient with a nonfunctioning gallbladder actually absorbs the contrast medium from the gastrointestinal tract. Cholografin is of assistance in these particular patients if calculi are outlined or if cystic duct obstruction permits only visualization of the common duct.

FIG. 1. Cholangiogram, after vagotomy and gastroenterostomy. The pronounced shadow cast by the duodenum 10 minutes after intravenous cholografin suggests that the inability to obtain a postoperative cholecystogram with priodax was the result of reduced tone of the sphincter of Oddi. Preoperative visualization with priodax had been normal.

Despite its disadvantages, cholografin possesses distinct advantages and diagnostic potentialities. Its primary importance lies in providing a dependable nonoperative method of obtaining a cholangiogram consistently, even in the absence of the gallbladder. This use of cholografin, together with its ability to outline large stones in the common duct, has been emphasized. Its application for

FIG. 2. The pyelogram obtained in patient A. C. (Table VI) was the most pronounced in this series. The biliary tree did not visualize although hepatic function studies revealed no abnormalities. Similar results were obtained when examination was repeated 3 weeks later.

successful visualization of small stones lodged in the terminal portion of the common duct presents a more difficult problem since this crucial area cannot be projected free from the duodenum. Although cholografin is valuable for cholangiography its use is probably limited by frequent failure to visualize small stones lodged in the distal portion of the common duct.

Until now, the suggestion that cholografin may aid in the diagnosis of acute conditions of the abdomen has not been evaluated. It was anticipated that this agent would contribute to the diagnosis of acute cholecystitis by demonstration of a cholangiogram in the absence of a cholecystogram, or by the demonstration of calculi. By this means cholecystic disease was diagnosed in 7 cases, while normal visualization occurred in 11 cases without this disease. Examination, therefore, proved helpful in the diagnosis of 18 acutely ill patients studied. A normal cholografin visualization of the gallbladder occurred in 1 patient with acute cholecystitis. Knowledge that the cystic duct was patent was helpful in the management of this patient. In the remaining 14 patients with acute cholecystitis or acute pancreatitis, the contrast medium failed to appear in any portion of the biliary tree. Silvani and McCorkle reported a similar experience in 11 cases of acute pancreatitis in which the gallbladders failed to visualize after intravenous iodeikon during the acute phase, but subsequently were shown to be normal at time of laparotomy or by cholecystogram after recovery.

In this series, it appears that the failure of cholografin visualization with acutely ill patients without jaundice was the result of abnormal hepatic function rather than a mechanical factor such as ileus of the biliary tree. The latter was suggested by Howard as the cause of nonvisualization of the gallbladder associated with nonspecific trauma. Our explanation is strengthened by the observation that initial nonvisualization was associated with elevated BSP, while visualization after recovery was associated with normal BSP. Cholografin might be of greater value in differentiating between acute pancreatitis and acute cholecystitis if the examination is made during an earlier phase in the disease before hepatic function is altered.

Impaired hepatic function and morphologic parenchymatous changes of the liver have been reported in patients with cholecystitis and pancreatitis. The pathogenesis for these changes is unknown. The effect of intra-abdominal inflammation on hepatic function is not limited to pancreatitis and cholecystitis, for hepatic dysfunction has been associated with acute appendicitis, perforated peptic ulcer, and other abdominal diseases. Our observations reveal that altered hepatic function studies were associated less frequently with the latter diseases than with the former. This relationship may be the result of a less severe inflammatory reaction located at a greater distance from

TABLE VI.—LIVER FUNCTION STUDIES IN PATIENTS NOT ACUTELY ILL AND WITH NONVISUALIZATION OF BILIARY SYSTEM WITH CHOLOGRAFIN

Patient	Diagnosis	Cephalin flocculation 24 hr.	Cephalin flocculation 48 hr.	Thymol turbidity	Alkaline phosphatase	Serum bilirubin, mgm. per cent	BSP retention, per cent
J.P.	Serum hepatitis (recovered)	neg.	neg.	12.0	12.9	1.04	8.4
A.F.	Laennecs cirrhosis	neg.	neg.	2.8	5.2	0.82	7.8
A.C.	Chronic cholecystitis	neg.	1+	6.2	6.7	1.24	5.1
A.D.	"Post cholecystectomy syndrome"	neg.	neg.	10.5	12.0	1.0	4.0
J.G.	Pancreatitis (recovered)	neg.	±	9.5	7.5	0.64	6.2

the liver, as in acute appendicitis, or the result of the patient seeking early medical attention, as in cases of perforated peptic ulcer.

The results of attempting to correlate cholografin visualization of the extrahepatic biliary tree with hepatic function suggests that cholografin visualization, in itself, may represent a sensitive hepatic function test. In 1925, Graham and Cole reported the use of sodium phenoltetraiodophthalein for simultaneous cholangiography and estimation of hepatic function. They stated that a normal gallbladder could be visualized in the presence of 60 per cent (6 times normal) retention of dye. Obviously, with this contrast medium the presence of a cholecystogram did not represent normal hepatic function. With cholografin, however, visualization of the extrahepatic biliary tree has not been obtained when the BSP retention was greater than approximately 15 per cent or the serum bilirubin above 3.0 milligrams per cent. There is no satisfactory explanation for the difference between the upper limits of BSP retention compatible with visualization in our cases and those of Wise and O'Brien who reported "good chance" of visualization with a BSP retention of 20 to 30 per cent in 40 minutes. The 5 cases in Table VI are further indication of the minimal alterations in hepatic function that may be associated with cholografin nonvisualization. It is doubtful that this material will be used deliberately to evaluate hepatic function. The presence of cholografin visualization, however, is a reliable indication that normal hepatic function exists.

SUMMARY AND CONCLUSIONS

Studies concerning the use of intravenous cholografin were performed on 56 patients.

1. An evaluation of the ability of intravenous cholografin to differentiate cholecystitis in the differential diagnosis of acute conditions of the abdomen in 34 cases is presented. The presence of a cholangiogram in the absence of a cholecystogram was associated with acute cholecystitis. Reliability of diagnosis was highest with patients ill less than 24 hours. Longer illness resulted in high incidence of nonvisualization of the biliary tract which was caused by acute idiopathic alterations in the hepatic function which were reversible and were of short duration.

2. Cholografin nonvisualization cannot be used alone to evaluate degree of hepatic dysfunction. These studies suggest, however, that the presence of cholografin visualization can be interpreted as the existence of normal hepatic function.

3. From a comparative study of oral and intravenous cholangiography in 22 cases the latter technique is not recommended for routine cholecystography. Rather it is suggested that cholografin may prove valuable when failure to obtain a cholecystogram results from inadequate absorption from the gastrointestinal tract or altered dynamics of the sphincter of Oddi. In such cases, cholografin is diagnostically helpful when cystic duct obstruction is present or calculi are visualized.

4. Cholografin is particularly valuable for visualizing calculi in the bile ducts. Its

inability adequately to visualize the terminal portion of the common duct, an area of critical importance, limits its usefulness for this purpose.

REFERENCES

1. Graham, E. A., and Cole, W. H. Roentgenologic examination of the gallbladder: preliminary report of a new method utilizing the intravenous injection of tetrabromphenolphthalein. J. Am. M. Ass., 1924, 82: 613–614.
2. Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S. Diseases of the Gallbladder and Bile Ducts. Philadelphia: Lea & Febiger, 1928.
3. Howard, J. M. Gallbladder function (cholecystographic studies) following nonspecific trauma. Surgery, 1954, 36: 1051–1055.
4. Silvani, H. T., and McCorkle, H. J. Temporary failure of gallbladder visualization by cholecystography in acute pancreatitis. Ann. Surg., 1948, 127: 1207–1211.
5. Wise, R. E., and O'Brien, R. G. Intravenous cholangiography. Surg. Clin. N. America, 1955, June: 755–763.

A NEW METHOD FOR SURGICAL CORRECTION OF TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY

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DURING THE PAST 3 YEARS, one of the major efforts in our experimental laboratory has been the development of a satisfactory method of correcting transposition of the aorta and pulmonary artery. Without going into tedious enumeration, suffice it to say that our experiments in approximately 150 dogs have generally paralleled those described by previous investigators, notably Blalock and Hanlon, Lillehei and Varco, Mustard and associates, Bjork and Bouckaert, and Albert. Our successes in applying those experiments to humans have been just as limited as those reported by these investigators. It was finally concluded that most approaches to this problem inadvertently impose severe surgical trauma upon the patient. We set out to find some compromise procedure which could be done in terms of smaller amounts of surgical manipulation. In our efforts, we drew heavily from the recorded experiences of these investigators.

On the basis of observations made upon our pathologic specimens of transposition of the aorta and pulmonary artery, we concluded that the best approach to the problem was transposition of the major veins at the base of the heart. Such an approach was applicable to most of the variations encountered, and considerable recorded clinical observation could be applied in its support. Lillehei and Varco had demonstrated that patients with transposition of the aorta and pulmonary artery live long enough, with the right pulmonary artery occluded, to permit doing the necessary venous anastomoses. Barring undue delay, congestion of the right lung during occlusion of its artery and veins should not occur. In addition, transfer of the veins, instead of the aorta and pulmonary artery, would eliminate the necessity for transferring the coronary arteries from the pulmonic to the systemic circulation. Two important problems remained to be solved: (a) It was necessary to determine how much of the venous return to the heart had to be transposed in order to relieve the patient's cyanosis. (b) The necessary procedure had to be broken down into a series of surgical maneuvers that could be done without upsetting the patient's physiologic processes beyond tolerance.

Our first clinical trial involved simple transfer of the right pulmonary veins to the right atrium. However, the degree of clinical improvement was unsatisfactory. We then attempted to transfer the superior vena cava to the left atrium, in conjunction with transposition of the right pulmonary veins to the right atrium. Two such clinical trials were completed—one using a temporary polyethylene shunt between the right atrium and the superior vena cava while the latter was being transposed to the left atrium, the other utilizing a homologous aortic graft between the superior vena cava and the left atrium. Both of these patients died in the immediate postoperative period of superior vena caval obstruction. It became apparent that the anatomic relations of the superior vena cava are such that it is readily compressed by the right main bronchus, the right pulmonary artery, and the transposed right pulmonary veins, as it passes between these

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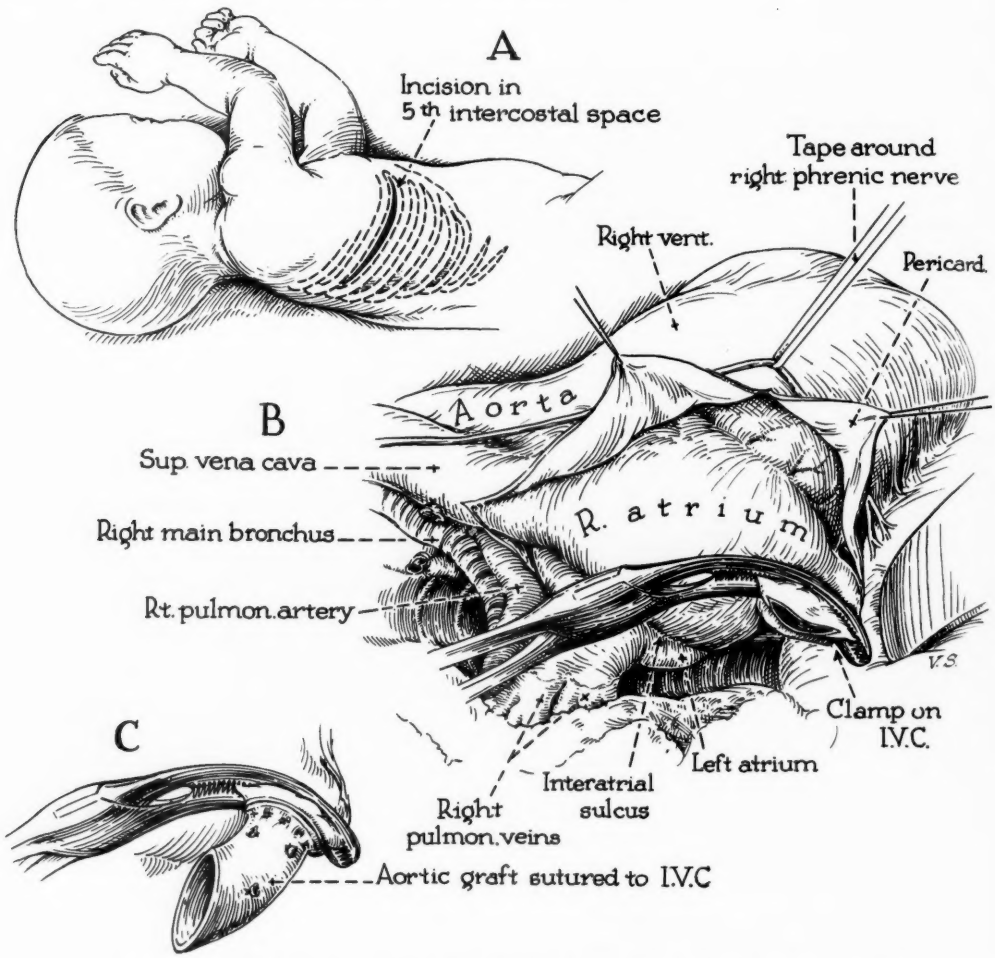


FIG. 1. A–H, Details of operative procedure utilizing a homologous aortic graft for transposition of the inferior vena cava to the left atrium, in conjunction with transfer of the right pulmonary veins to the right atrium. (See text.)

structures to the left atrium. It was concluded that the inferior vena cava would have to be utilized, in spite of its extremely short length in humans. The inferior vena cava is in such a position that no other structures will compress it after it is transferred to the left atrium. In addition, the amount of blood returning to the heart through the inferior vena cava is approximately the same as the amount of blood delivered through the right pulmonary veins, so that the systemic and pulmonic circulations tend to remain balanced after transposition of these major veins. The final operation, as it was worked out in the experimental laboratory, may be described as follows.

OPERATIVE PROCEDURE

A thoracotomy is performed through the right fifth intercostal space, and the right pulmonary artery, both right pulmonary veins, and the inferior vena cava are dis-

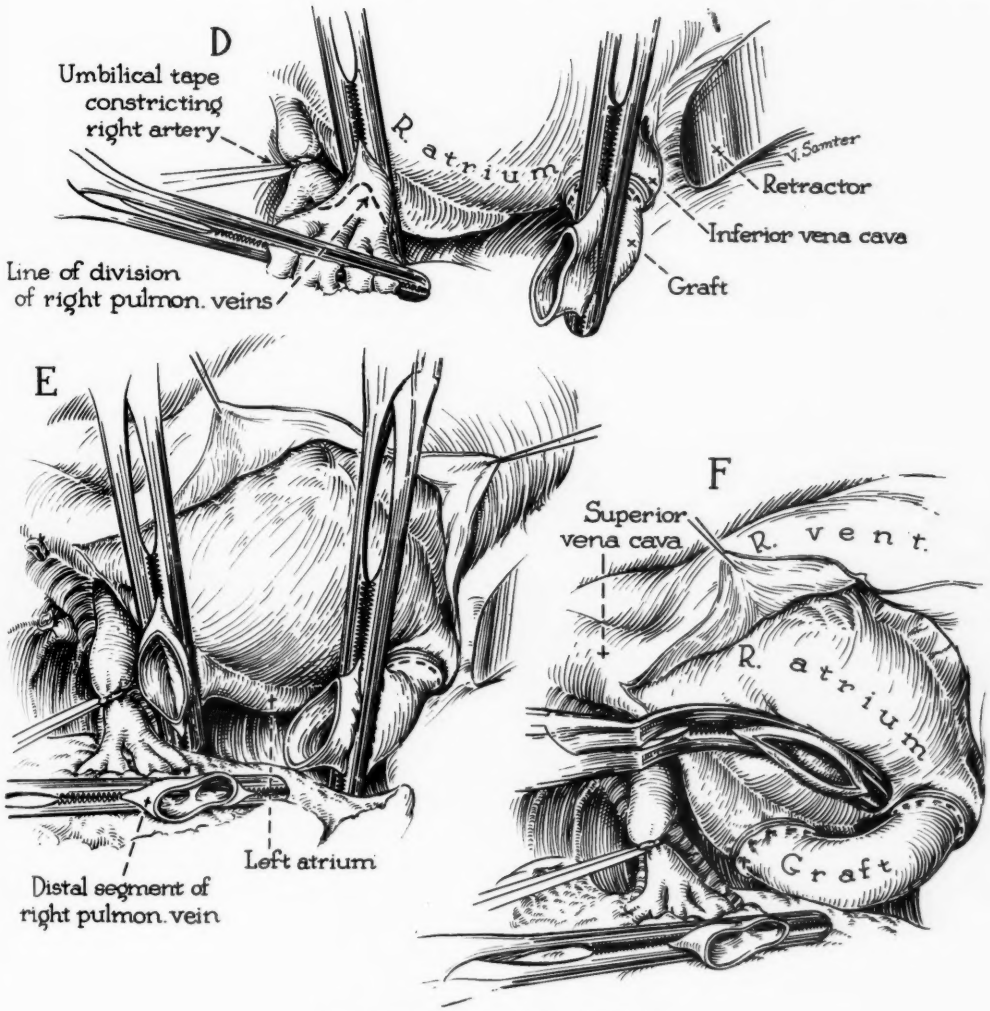


FIG. 1, continued. (G and H on page 230.)

sected free (Fig. 1A). The pericardium is opened during the dissection, exposing the lateral aspect of the right atrium. A curved coarctation clamp is placed on the lateral aspect of the inferior vena cava in such a way that the flow of blood through the inferior vena cava into the right atrium is not occluded (Fig. 1B). A longitudinal incision is made in the lip of the inferior vena cava held within the coarctation clamp, and the larger end of a suitable homologous aortic graft is anastomosed to the edges of the incision. A continuous everting type of arterial suture is used in order to decrease thrombus formation (Fig. 1C).

After completion of the anastomosis, an angulated ductus forceps is placed near the open end of the aortic graft and the curved coarctation clamp is removed from the inferior vena cava. The open end of the graft is trimmed and bevelled to fit against the proposed left atrial stump of the right pul-

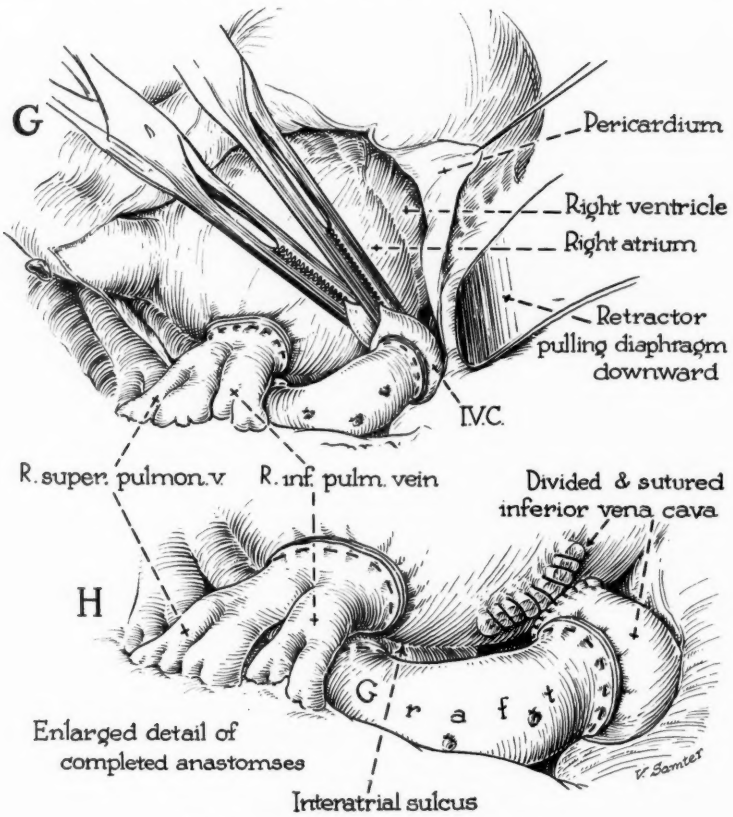


FIG. 1, continued. (Legend on page 228.)

monary veins. The right pulmonary artery is then occluded with umbilical tape and the right pulmonary veins are divided between straight coarctation clamps in such a way that both pulmonary venous ostia open upon a single pedicle (Fig. 1D). The placing of the straight coarctation clamps before division of the pulmonary veins is important. The distal coarctation clamp is placed longitudinally, so that it can later be easily apposed to the side of the right atrium. The proximal coarctation clamp is placed horizontally, facilitating its apposition to the angulated ductus clamp across the open end of the aortic graft (Fig. 1E). The open end of the aortic graft is then sutured to the stump of the left atrium with a continuous everting suture (Fig. 1F). After hemostasis is secured, the proximal coarctation clamp and the angulated ductus clamp are removed, permitting blood to flow from the inferior vena cava into the left atrium. Note that the attachment of the inferior vena cava to the right atrium has not yet been divided, so that there is no danger of imbalance of the systemic and pulmonic circulations.

A portion of the lateral wall of the right atrium is then excluded within a curved coarctation clamp and incised longitudinally (Fig. 1F). The distal straight coarctation clamp is apposed to this incision and the right pulmonary veins are anastomosed to the edges of the incision with a continuous everting suture. As soon as hemostasis is secured, the coarctation clamps are removed and the occluded right pulmonary artery is

released. The patient is then allowed to recover from the occlusion of the right pulmonary artery, before separation of the inferior vena cava from the right atrium is undertaken. A few moments later, the attachment of the inferior vena cava to the right atrium is divided between angulated ductus clamps, making the flow of blood from the inferior vena cava through the aortic graft and into the left atrium obligatory (Fig. 1G). The stumps of the inferior vena cava and the right atrium are oversewn with continuous arterial silk sutures and released (Fig. 1H). The right lung is allowed to expand and the thoracotomy is closed in the usual manner (Fig. 2).

In addition to the animals expended for development of technical details, this procedure was further substantiated by several sets of dog experiments: (a) Attempts in 12 dogs to divide and reanastomose the inferior vena cava proved that it was impossible to transfer the inferior vena cava directly to the left atrium. The length of time required for anastomosis exceeded the safe interval for caval occlusion in most of the dogs. They died of liver or renal failure by the fourth postoperative day. (b) Numerous types of temporary shunts were developed to keep the inferior vena cava draining into the right atrium during direct transfer of the cava to the left atrium. None proved adequate. (c) Finally, a homologous aortic graft was used to connect the inferior vena cava with the left atrium, as described. This procedure proved eminently successful, especially when the ascending aortic arch or the upper descending thoracic aorta was used for grafting. The elastic tissue in such aortic homografts kept the shunt open in spite of the low hydrostatic pressure in the inferior vena cava. (d) Twelve dogs were subjected to the proposed operation in sham. A homologous aortic graft was anastomosed from the inferior vena cava to the right atrium, and the right pulmonary artery and veins were clamped for the time required to transfer the inferior vena cava to the left atrium and the right pulmonary veins to the right atrium.

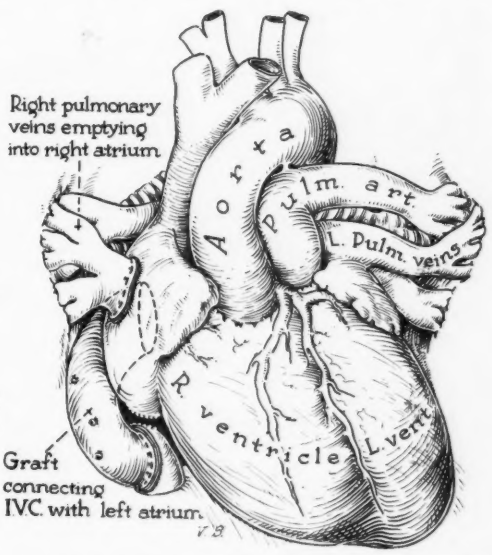
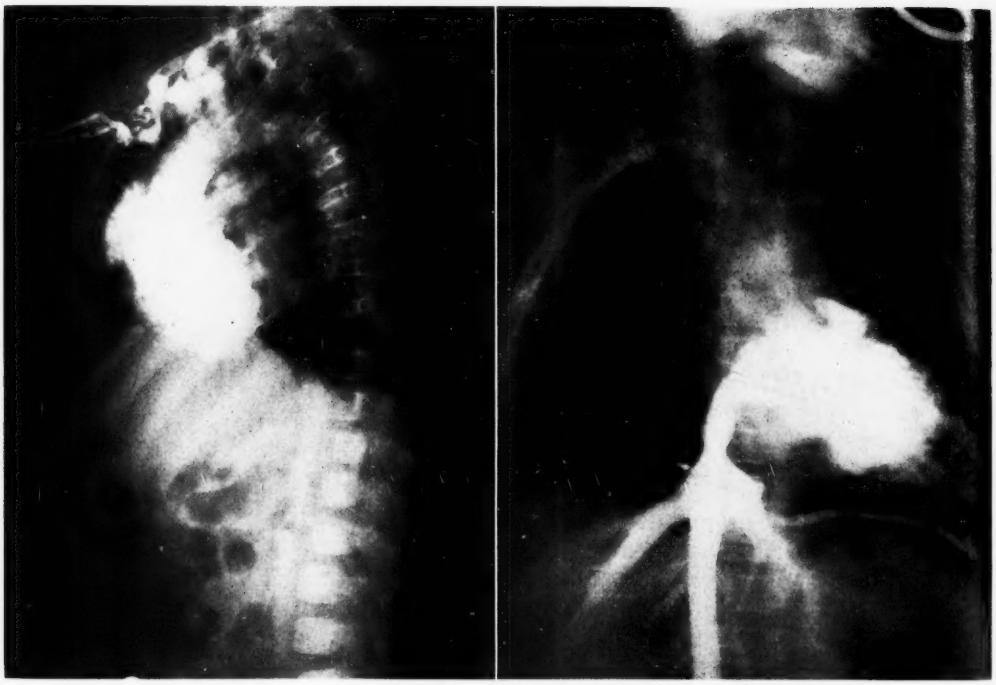


FIG. 2. Diagram of completed transfer of the inferior vena cava and the right pulmonary veins. Blood from the inferior vena cava empties into the pulmonic circulation via the left atrium. Blood from the right pulmonary veins empties into the systemic circulation via the right atrium.

The normal attachment of the inferior vena cava to the right atrium was then divided, making the flow of blood from the inferior vena cava into the aortic homograft obligatory. All the dogs withstood the procedure well. They have been allowed to survive for the past 8 months in order to ascertain the fate of the aortic grafts. Some of these animals have been sacrificed. The rest have been checked by venous angiography. In all, the grafts have remained patent and carry the caval stream to the atrium without any obstruction. (e) In order to determine the reaction of the graft to growth, the sham operation was done in a puppy weighing 8 pounds. The dog has now grown to a body weight of 40 pounds, and venous angiography reveals adequate function of the graft without significant narrowing. The operation was then given a clinical trial.

CASE REPORT

L. K. was first admitted to the hospital on December 16, 1952, at 1 year of age, with a history of cyanosis since birth. The cyanosis was increased by exercise.



a b

FIG. 3. Venous angiocardiograms of the patient before and after operation. a, Preoperative angiocardiogram via the antecubital vein shows blood from the superiorvena cava entering the right atrium then being ejected by the right ventricle into the aorta. These are typical findings of transposition of the aorta and pulmonary artery. b, Postoperative angiocardiogram via the saphenous vein showing blood from the transposed inferior vena cava entering the left atrium and being ejected by the left ventricle into the pulmonary arteries. Note that the homologous aortic graft connecting the inferior vena cava with the left atrium is patent and functioning adequately 3 months after surgery.

Physical examination revealed a soft systolic murmur heard best at the fourth left intercostal space near the sternum. The lungs were clear. The liver margin was palpable just below the costal margin. Roentgenograms of the chest revealed normal vascularity of the lung fields and mild enlargement of the heart. Initially, a diagnosis of tetralogy of Fallot was entertained.

During the next year, however, the patient's cyanosis and dyspnea became more intense. The enlargement of the heart and the vascularity of the lung fields increased. By 2 years of age, the patient had begun to have periods of unconsciousness precipitated by crying or other forms of exertion. She was unable to walk or stand. The liver edge had become palpable 5 centimeters below the costal margin and was tender. Angiocardiography established the diagnosis of transposition of the aorta and pulmonary artery, and she was admitted on March 21, 1955 for its surgical correction. Her preoperative red blood cell count was 8,410,000 per cubic millimeter with a hemoglobin of 16.0 grams per 100 cubic centimeters. She was in severe cardiac failure. Surgery had to be postponed for 4 weeks, until she could be digitalized and her condition could be improved by bed rest.

On May 6, 1955, a right thoracotomy was performed and the right pulmonary veins and the inferior vena cava were transposed as described in detail in the foregoing. The patient had a satisfactory postoperative course. Definite improvement in color was noted in the immediate postoperative period, but mild cyanosis persisted at the time of discharge from the hospital on May 31, 1955. Three months after operation she was readmitted to the hospital for study. The red blood cell count had fallen to 7,170,000 per cubic millimeter and the hemoglobin had fallen to 15.3 grams per 100 cubic centimeters. She was essentially acyanotic at rest and there was a slight suggestion of cyanosis with exercise. No episodes of unconsciousness had occurred since operation. She had begun to walk for the first time in her life and showed marked

improvement in mental alertness. Venous angiograms were done on August 3, 1955. They showed that the aortic graft was functioning well and that the blood from the inferior vena cava was emptying adequately into the left atrium (Fig. 3).

The patient's response to this operation has been extremely gratifying, particularly in view of the fact that it was done with ordinary cardiovascular techniques. Although the cyanosis has not been completely relieved, it is hardly detectable at rest. On exercise, there is only slight increase in cyanosis and there have been no episodes of unconsciousness or dyspnea. Muscular activity has increased and should continue to improve as the patient develops muscle mass and muscular co-ordination that have been dormant for the first 4 years of her life. The heart size has decreased. Cardiac failure has not recurred postoperatively.

Although this procedure certainly is not the final answer to transposition of the aorta and pulmonary artery, it may provide an opportunity to rescue some of these patients. Success in this initial patient justifies further clinical trial. Should any significant symptoms persist after the operation described, it is planned to extend the transposition of the major veins to the heart by performing a second stage thoracotomy on the left side and inserting a homologous aortic graft from the left innominate vein to the left atrium, in order to transpose the blood of the superior vena cava to the pulmonic circulation. An attempt could be made at the same time to transpose the left pulmonary veins to the coronary sinus. Should the coronary sinus be too small, inability to transfer the left pulmonary veins would not detract from the value of the second stage procedure, because it is known that patients with partial anomalous pulmonary venous return usually have excellent longevity and few clinical symptoms. At any rate, present indications are that the symptoms of transposition of the aorta and pulmonary artery will probably be sufficiently improved after the initial right thoracotomy so that a second stage thoracotomy may not be necessary.

SUMMARY

1. A new technique is described which utilizes a homologous aortic graft to transpose the inferior vena cava and the right pulmonary veins for partial correction of transposition of the aorta and pulmonary artery.

2. Successful application of this technique in one patient is presented. The patient's symptoms were remarkably improved postoperatively. Venograms show excellent function of the graft 3 months after surgery. Similar grafts in dogs have been followed for 8 months and are functioning well.

3. The operative procedure is described in detail. A number of experiments used to verify various aspects of the procedure are described.

REFERENCES

1. ALBERT, H. M. Surgical correction of transposition of the great vessels. Surgical Forum 1954; American College of Surgeons. P. 74. Philadelphia: W. B. Saunders Co., 1955.
2. BJORK, V. O., and BOUCKAERT, L. Complete transposition of the aorta and the pulmonary artery; an experimental study of the surgical possibilities for its treatment. J. Thorac. Surg., 1954, 28: 632.
3. BLALOCK, A., and HANLON, C. R. The surgical treatment of complete transposition of the aorta and the pulmonary artery. Surg. Gyn. Obst., 1950, 90: 1.
4. LILLEHEI, C. W., and VARCO, R. L. Certain physiologic, pathologic and surgical features of complete transposition of the great vessels. Surgery, 1953, 34: 376.
5. MUSTARD, W. T., CHUTE, A. L., KEITH, M.D., SIREK, A., ROWE, R. D., and VLAD, P. A surgical approach to transposition of the great vessels with extracorporeal circuit. Surgery, 1954, 36: 39.

ROENTGEN DIAGNOSIS OF SPONTANEOUS INTERNAL BILIARY FISTULAS AND GALLSTONE ILEUS

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IT IS THE PURPOSE of this report to stress the very characteristic clinical and roentgen findings in cases of internal biliary fistula and gallstone ileus. The tendency to minimize the role of the roentgen study in resolving these problem cases must be re-evaluated. In present day radiologic practice, the diagnosis of biliary fistulas and gallstone ileus is made with increasing frequency. In a review of 20 cases of internal biliary fistula from the files of Meadowbrook Hospital, comprising the basis for this publication, 13 (or 65 per cent) were diagnosed prior to surgery. Ten of these cases were associated with gallstone ileus and the correct diagnosis was made preoperatively in 8 instances, or in 80 per cent.

The subject of internal biliary fistula and gallstone ileus has received considerable attention in the literature. The pathologic anatomy may be briefly summarized by stating that these fistulas are the result of perforation of the gallbladder or common duct into the duodenum, less commonly into the colon, and occasionally into the stomach. This condition is usually produced by a stone causing inflammation and erosion, leading to a gangrenous gallbladder wall. Fibrosis, shrinkage, and thickening may follow. It must be remembered that perforating neoplasms of the colon, pancreas, or biliary tract may also produce fistulas. Perforated duodenal ulcers are responsible for most of the choledochoduodenal fistulas, though a smaller number may represent unusual complications of impacted stones in the common duct.

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Clinically these patients present a striking similarity in their medical background. Most of the patients are female (16 of the 20 cases in our series). The 10 patients with gallstone ileus were all women. The patients are obese and usually in the older age group (an average of 72 years in the 20 patients). A past history of gallbladder disease can usually be elicited and sudden relief from pain may establish the time of formation of the fistula. Eighteen of the 20 patients were admitted with abdominal pain. In 14 there were frank obstructive symptoms varying from 1 day to 2 weeks in duration. Those patients who subsequently proved to have gallstone ileus were admitted with obstruction and the symptomatology here averaged 1 week in duration.

ROENTGEN ASPECTS

Gas in the biliary tree. The presence of gas in the biliary tree is generally accepted as evidence of a biliary fistula. Radiolucent streaking or irregular pockets of gas in the right upper abdominal quadrant suggest the diagnosis (Fig. 1). Gas was present in 9 of the 20 cases of internal biliary fistula of this series and in 5 of the 10 cases of gallstone ileus.

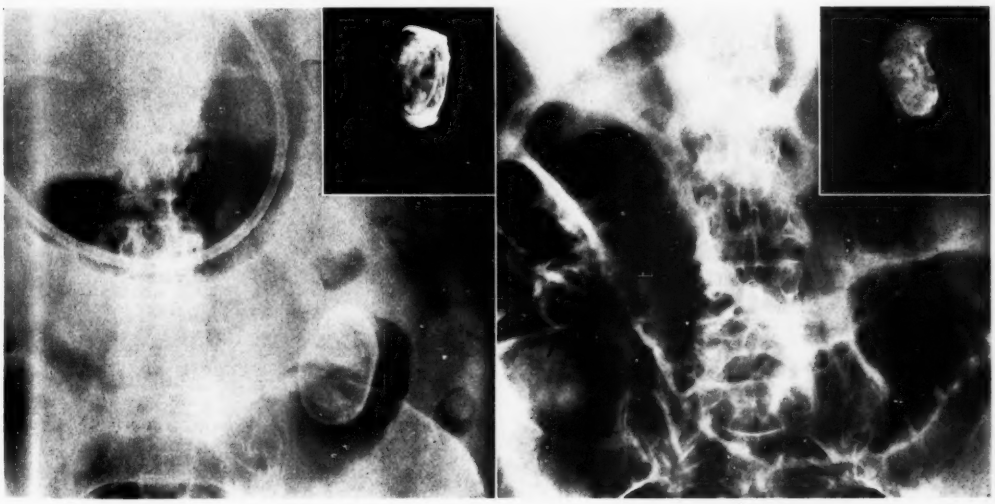
Biliary calculi. The aberrant calculus in the presence of gallstone ileus, may be found anywhere in the abdomen, though most frequently in the right and left lower quadrants and usually in association with a dilated loop of bowel (Fig. 2a and 2b). These stones vary in size from 2.0 to 6.0 centimeters in diameter and may be but faintly calcified, making their detection difficult. It has been found that round stones are more apt to cause lif-

ficulty than oval stones and irregular ones more apt to be caught in mucosal folds than smooth stones. Faceted stones are apt to be multiple. Sixteen of the 20 cases of internal biliary fistulas in this series were associated with stones. One was passed by rectum and 12 were found at surgery—9 in the ileum, 1 in the liver, and 2 in the duodenum. In 3 cases, more than 1 stone was present. In the 10 patients with gallstone ileus the stones were seen on the roentgenograms in 5 instances.

Bowel patterns as seen on abdominal scout films. In the 20 patients with internal biliary fistulas, scout films showed the following: 8 cases of small bowel obstruction, 1 case of large bowel obstruction, 2 cases of gastric dilatation, 6 cases with no intestinal obstruction, 1 film unsatisfactory, and 2 cases in which no scout films were taken.

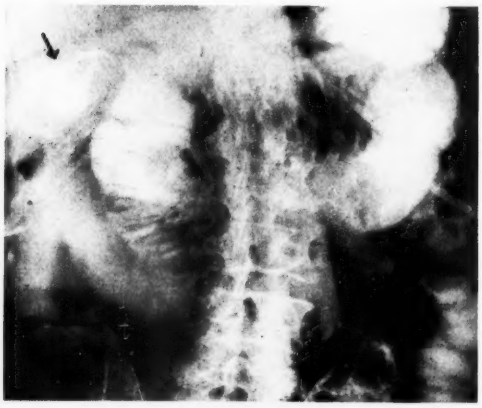
Gastrointestinal series. Oral barium is occasionally used to locate a point of obstruction when the large bowel is reasonably excluded as the obstructing site. The demonstration of a fistula in this fashion may be difficult. The communication is more readily shown via the barium enema route in cases of cholecystocolic fistula. In 5 cases in this series a gastrointestinal series was carried out; in 4, a diagnosis of cholecystoduodenal fistula was made (Fig. 3a), and in 1 case a choledochoduodenal fistula (Fig. 3b) was found. In another case the gallstone was found lodged in the duodenal bulb (Fig. 3c).

FIG. 1. A markedly dilated common duct is outlined by gas.



a b

FIG. 2. a, Gallstone ileus in a 65 year old female. The stone was lodged in a loop of ileum. The surgical specimen (insert) measured 6.0 by 4.0 by 4.0 centimeters. b, Gallstone ileus in a 86 year old female. The stone seen in the right upper abdomen was in the ileum. The surgical specimen (insert) measured 3.0 by 5.0 centimeters.



a

b

c

FIG. 3. The value of the barium meal in diagnosing biliary fistulas and gallstone ileus is shown in the following cases: a, Female, aged 75 years. The gallbladder has filled with barium (upper arrow). The calculus (2.0 by 2.8 centimeters), producing ileus, is seen in the left mid abdomen (lower arrow). b, Female, aged 72 years. The barium has filled a dilated common duct which contains stones. The pocket of barium just above the bulb is believed to be due to a perforated duodenal ulcer. This is an example of a choledochoduodenal fistula. c, Female, aged 61 years. The barium meal shows a radiolucent biliary calculus filling the duodenal bulb. The calculus measured 3.0 by 2.0 centimeters.

Barium enema examination. Gallstones not infrequently lodge in the large bowel, and the barium enema study may show the point of obstruction as well as the stone itself. The contrast material may enter the gallbladder or an abscess pocket, or may extravasate into the peritoneal cavity. It should be remembered that large bowel neoplasms as well as neoplasms of the gallbladder may cause biliary fistulas (Fig. 4). Gallstones frequently become lodged at the site of diverticulitis and such a finding is shown in Figure 5a and b.

Extra-alimentary calculi. Gallstones have been reported in almost every location in the

FIG. 4. Cholecystocolinic fistula demonstrated by barium enema. Male, aged 79 years. This patient had a carcinoma of the gallbladder. A postevacuation film shows the complete obstruction encountered fluoroscopically. Barium is seen in the gallbladder and outlining the valves of Heister.

FIG. 5. a, Female, aged 79 years. The postevacuation enema study shows the gallstone (lower arrow) in an area of diverticulitis. Gas is seen in the biliary tree (upper arrow). The specimen which was passed by rectum (insert) measured 3.0 by 4.0 centimeters. b, A barium enema in the same patient, performed after passage of the stone, shows the shrunken gallbladder filled with barium.

FIG. 6. a, Female, aged 63 years. The abdominal scout film prior to surgery shows the calcification in the right upper quadrant. This was interpreted as calcification in the wall of the gallbladder around a large calculus. b, In the same patient, a cholangiogram after cholecystectomy still shows the calcified structure (identified as a calculus at surgery) imbedded in the liver substance.

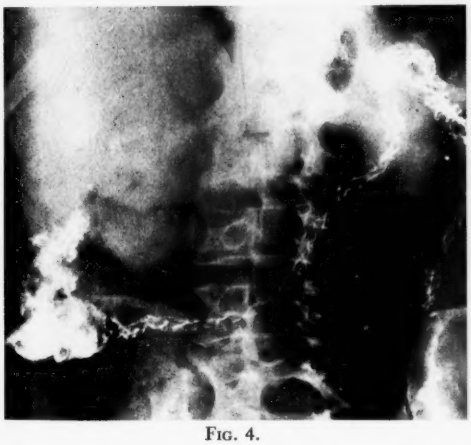
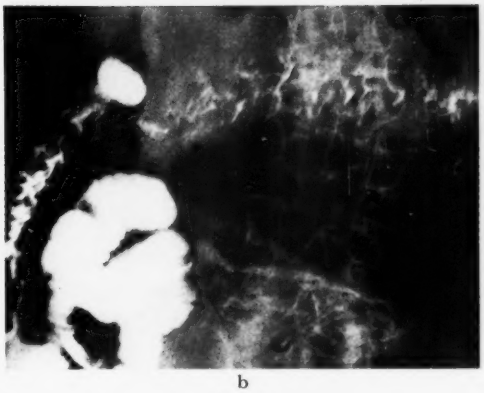


FIG. 4.

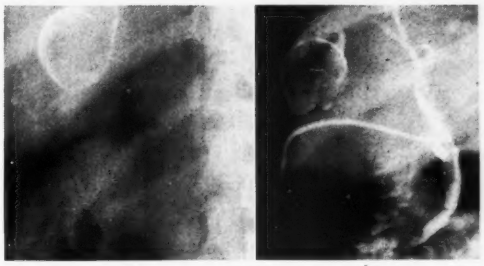
a



b

FIG. 5.

chest and abdomen. Their recognition is usually not difficult, though their differential diagnosis must exclude bladder calculi, kidney stones, calcified lymph nodes, and calcified epiploic appendages. We have recently seen a patient with bilateral ovarian teratomas presenting 2 round, faintly calcified structures in the pelvis, and aberrant gallstones were difficult to exclude in this case. To find the stone imbedded in the liver substance (Fig. 6) was also unusual and has not



a b

FIG. 6.

been previously described in the literature reviewed for this publication.

Roentgen accuracy in cases of gallstone ileus. The combination of roentgen findings which enabled the examiner to arrive at the correct diagnosis 8 times in the 10 cases of gallstone ileus are tabulated below:

3 cases: small bowel obstruction, gas in the biliary tree, and gallstone in aberrant location
2 cases: small bowel obstruction and aberrant gallstone
2 cases: small bowel obstruction and gas in the biliary tree
1 case: large bowel obstruction and gas in the biliary tree
1 case: bowel obstruction clinically and demonstration of a fistula by gastrointestinal series
1 case: small bowel obstruction without gas or stone; the clinical setting was so typical that a diagnosis of gallstone ileus was suggested preoperatively

CONCLUSIONS

In the past, the radiologic diagnosis of internal biliary fistulas and gallstone ileus was infrequently made, probably because of insufficient awareness of the classical clinical picture presented by these patients. The radiologist was apt to overlook the presence of gas in the biliary passages and would therefore neglect to search for a faintly calcified aberrant calculus on the abdominal scout film.

The diagnosis of gallstone ileus is suggested in the presence of the following: (1) intestinal obstruction; (2) an obese female in the seventh decade; (3) a past history of gallbladder disease, frequently associated with heart disease and diabetes (a recent episode of illness attributed to viral infection may be offered); (4) the abdomen free of scarring from previous surgery; (5) the scout film showing gas in the biliary passages; (6) the calculus itself anywhere in the abdomen.

With greater attention to clinical findings and careful scrutiny of related roentgen studies the radiologist is in a position to play an important role in the successful resolution of these interesting diagnostic problems.

EDITORIALS

MASSIVE GASTROINTESTINAL HEMORRHAGE

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REGARDLESS OF THE MOUNTING INTEREST of internists and surgeons alike in the proper management of gastrointestinal hemorrhage, the mortality from massive hemorrhage remains alarmingly high. Because the emergency nature of this ailment has concentrated the greater number of cases in large institutions with an attached emergency service, only a few practicing physicians have had a sufficient experience with massive bleeding to consider it a problem of major importance. The personnel of most large institutions are confronted constantly with the problems of diagnosis and treatment in the exsanguinated patient and are prepared for them; elsewhere, lack of experience usually results in confusion and unnecessary delay in proper management which contribute appreciably to the high mortality.

Although there are a variety of diseases that will cause serious gastrointestinal bleeding, the great majority are due to peptic ulceration of the stomach or duodenum or to ruptured gastric or esophageal varices. Of these, duodenal ulcer is the most common offender.

It is possible to elicit a definite history of peptic ulcer or cirrhosis in many patients who bleed and in this group the source of the hemorrhage may be reasonably certain. However, it is not always possible to elicit a useful history. Frequently, the patient in the greatest need of an early diagnosis and emergency treatment is the least able to give an accurate history. Without this, the diagnosis may become extremely difficult and the course of treatment to be undertaken equally uncertain.

Although a variety of criteria have been used to predict which of these patients will stop bleeding and which will not, none except the age of the patient seems to be at all reliable. While it is true that only rarely does a patient under 40 years of age bleed to death and that the likelihood of fatal hemorrhage increases with age thereafter, this observation does not preclude the possibility of fatal hemorrhage in the young nor eliminate the possibility of recovery in the aged.

Even though the source of hemorrhage on the basis of history alone may be reasonably clear, it should be noted that serious bleeding in the cirrhotic is not necessarily from a varix. Gross or even fatal bleeding from a peptic ulcer is not uncommon in the patient suffering with cirrhosis of the liver. This observation serves only to make the question of management more difficult. It is helpful, however, to note that even though hematemesis does not always accompany hemorrhage from duodenal ulcer and bleeding varices, the vomiting of blood almost certainly means that the site of bleeding is from a point somewhere above the ligament of Treitz. On the other hand, bleeding from the rectum, even though bright red in character, may have had its origin from any point in the gastrointestinal tract and, therefore, does not rule out upper tract bleeding.

Usually it is not difficult to distinguish between upper and lower tract bleeding, but it is impossible frequently to be certain of the exact source in either category. If the source is not evident from the history, clinical findings, and previous roentgenograms, carefully conducted x-ray and endoscopic examinations during the acute stage of bleeding often are distinctly helpful in the diagnosis and may be performed without undue hazard to the patient.

In view of the inherent difficulties in diagnosis and the ever present danger of exsanguination in patients over 40 years of age, what policy of management should be adopted? The following methods are to be considered: (1) conservative medical management of all gastrointestinal bleeders, regardless of age, duration of bleeding, and amount of bleeding; (2) early operative intervention in all patients with serious hemorrhage who are thought to be bleeding from a gastric or duodenal ulcer or neoplasm; (3) careful selection of patients for each of these categories.

Although each of these methods of management has been reported to be successful, it is clear that the method to be selected necessarily must be adapted to the personnel and other facilities available. A method adaptable in one institution cannot always be applied to another.

The conservative management of all bleeders to be reasonably successful requires proper laboratory facilities and the availability of a sufficient amount of whole blood for continual and repeated replacement therapy, while the introduction of surgery as a means of treatment presupposes a team skilled in diagnosis, resuscitation, anesthesia, and surgical technique. For these reasons, each physician and each institution in anticipation of the care of a patient suffering with massive gastrointestinal hemorrhage should adopt a policy of treatment commensurate with the facilities and personnel available to them and the internist and the surgeon responsible for the patient must be in constant attention.

Most observers agree that the following points are pertinent: (1) Massive gastrointestinal hemorrhage may be and often is fatal. (2) Fatal hemorrhage is uncommon in patients under 40 years of age, but increases with the age of the patient thereafter. (3) Fatal hemorrhage can occur in any episode of bleeding. (4) The patient who continues to bleed under adequate blood replacement therapy is apt to bleed to death and should be considered a candidate for surgery. (5) The patient who stops bleeding and then starts again under adequate medical management is also apt to bleed to death and should be considered a candidate for emergency surgery.

It is not the purpose of this communication to outline in detail methods of diagnosis and treatment, but rather to emphasize the dangers of massive gastrointestinal bleeding and its grave prognosis and to urge that all doctors and institutions adopt and be prepared to institute a policy of treatment commensurate with the facilities and personnel available to them.

BLOOD REPLACEMENT THERAPY—USE AND ABUSE

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IT HAS LONG BEEN RECOGNIZED that every surgical patient with a chronic infection, just as every surgical patient with malignant disease, is anemic. It has also long been recognized that even in surgery of limited extent, shock is always a possibility in the anemic patient, both at operation and immediately thereafter, and that the shock may be fatal. Considerably more infrequent is the recognition that the essential deficit is not in hemoglobin or red blood cells but in the blood volume and the total circulating hemoglobin. Also more recent is the recognition that these deficits can be precisely demonstrated only by special techniques of blood volume determination.

These tests are not simple, but they are perfectly practical for general use. They can be learned efficiently and carried out accurately without too much difficulty, even in small hospitals. The will to institute them and to continue to perform them is perhaps the most important consideration. Their greatest usefulness, as has been repeatedly pointed out, is that they demonstrate a breakdown in compensation that escapes clinical detection but that significantly influences the morbidity and mortality after surgical intervention. The reason is that tests of volume substitute factual data for clinical impressions.

Surgery has not, of course, become entirely dependent upon the laboratory. The clinical evaluation alone is frequently out of line with precise laboratory data, and may be widely wrong. The clinical evaluation of the patient is still important. One is unlikely to operate on clinically poor risks, or even fair risks, without blood replacement, but it is easy to operate on patients who seem, though deceptively, to be good risks. On the basis of clinical evaluation alone, patients with blood deficits may receive no blood at all, or less than they need, or more than they need, while patients with no deficits may receive blood that they do not need, sometimes in considerable excess.

Patients whose nutritional status has been seriously impaired demand special consideration; the error in their management is particularly dangerous because it is insidious. Blood volume must be calculated on the basis of optimal weight in health, and blood replacement must be on the same basis. Blood replacement must usually be continued after operation, for there is often a considerable, and occasionally a frightening, drop in postoperative blood volume values, in spite of liberal blood replacement before and during operation. If no complications occur, these patients usually recover, though their wounds may heal slowly and their convalescence is prolonged. Postoperative hemorrhage or other serious complications, however, often go hard with them.

Similarly, the postoperative drop in elderly patients is likely to be marked in both benign and malignant disease, even in patients fortified by preoperative transfusion up to the limit of demonstrated deficits. The elderly patient, for that matter, always presents a special problem. His margin of reserve is slim. He compensates slowly. There is no room in his case for correction of errors inherent in crude replacement therapy. He can die promptly from cardiopulmonary causes and peripheral vascular collapse. Yet the blood that he is given must be on the basis of absolute needs. Overloading of the circulation is a possible risk at any age. It is particularly dangerous in elderly patients because it can occur so insidiously. A therapeutic death is sometimes the direct result of the therapy designed to save the patient's life.

The surgically significant feature of a reduced blood volume, as has already been pointed out, is increased susceptibility to shock, manifested by what has been well termed an "unsteady" state. It is a matter of the greatest importance to keep the blood pressure stable during surgery. No operation of magnitude should be undertaken without an adequate quantity of whole blood immediately available and employed as necessary in the light of events.

It is equally important, however, that blood be given before operation, on the basis of actual blood volume determinations when possible, otherwise on the basis of a careful clinical evaluation of the surgical risk. It is tempting, when blood is in short supply, to reason that whatever deficit may exist can be made up at operation. The premises are faulty. Blood replacement on the operating table does not protect the patient against possible shock and hemorrhage during the early operating period, before the necessity for it becomes evident and blood can be run into the veins. Nor does it protect the patient against the anoxic changes which can occur during this period. Every surgeon can recall patients who, because of massive and unexpected hemorrhage, would not have lived to be taken off the operating table, in spite of quantities of blood given when the hemorrhage occurred, if they had not gone to surgery well fortified against just such accidents. Finally, blood given in an emergency must always be run in rapidly, with the risk, just discussed, of fatal overloading of the cardiovascular system, especially in older patients.

The magnitude of all surgery has greatly increased in the last several years. Surgical procedures of magnitude have increased in frequency. Operations are undertaken today which 10 or 20 years ago would not have been undertaken at all. Surgery is being performed on patients who formerly would have been refused whatever it had to offer because operation would have amounted to legalized execution. Yet in spite of this liberalization of indications, deaths from shock are now the exception in properly conducted hospitals. The anesthetist's chart on a properly prepared patient will show practically straight lines for the pulse and pulse pressure during surgery, with none of the precipitous dips that, even if they are corrected, often presage postoperative disaster.

We must not, however, permit ourselves to become so fascinated with the enormous benefits of parenteral therapy that we overlook certain essential facts. One is that oral alimentation is still the most effective way of building up a patient, though it sometimes takes more time to persuade him to eat than it does to give him a transfusion.

A fundamental fact about the use of blood, and one that sometimes seems to be forgotten, is that it is a medical commodity which will probably always be in short supply. In 4½ years of a war that threatened the very existence of this nation, and with the invocation of all possible elements of legitimate publicity, the American Red Cross was still able to collect less than 13,000,000 pints. In time of peace, blood is even harder to come by.

It should therefore be used with discretion and care, with due relation to the disease present and the patient's necessity. It should not be omitted when it is necessary. It should not be ordered as an almost automatic gesture. It should not be given when it can do no good. It should not be used to compensate for surgical errors and inexperience. It should not be ordered, even for surgical patients, whose anemia is due to diseases for which other forms of therapy are more efficient. Iron, liver extract, vitamin B_{12}, and folic acid are more efficient in some diseases than is blood, large quantities of which are frequently wasted under these circumstances.

Another error that should be avoided in this connection is the administration of blood in quantities in which it is not needed. Blood volume studies have clearly shown that a patient with a preoperative excess fares no better during or after operation

than a patient whose blood supplement is merely equal to his needs. Furthermore, the hazards that still attend transfusion, in spite of modern technical advances, should in themselves be a contraindication to its employment when it is not indicated. Several centuries ago patients were killed by having blood removed from them in the name of therapy, while today some are dying, also in the name of therapy, from excessive or unnecessary amounts of blood put into them.

Finally, there arises the question of what should be done for patients whose state is clearly hopeless if not actually terminal. Is it to their own best interests, is it fair to others who need the limited supplies of blood, is it even humane, to give blood to them? Sometimes this form of therapy is perfunctory and thoughtless. Sometimes it is humanely inspired. It is always as wasteful as it is futile. There is no lack of compassion in such a point of view.

The solution of the wise use of blood replacement is, of course, to treat the patient, not his hemoglobin level, or his blood count, or even his circulating blood volume, useful as is the knowledge of these data in the therapeutic scheme. The status of the individual patient depends upon his disease and its course. If he is to receive the best possible treatment, he must be considered as an individual and treated in the light of his special needs. Clinical evaluation, in short, is still a priceless tool, though it does not alter the practical usefulness of knowing the difference between the normal and actual blood values, so that any deficit which exists can be made up by the measured preoperative, operative, and postoperative transfusion of whole blood.

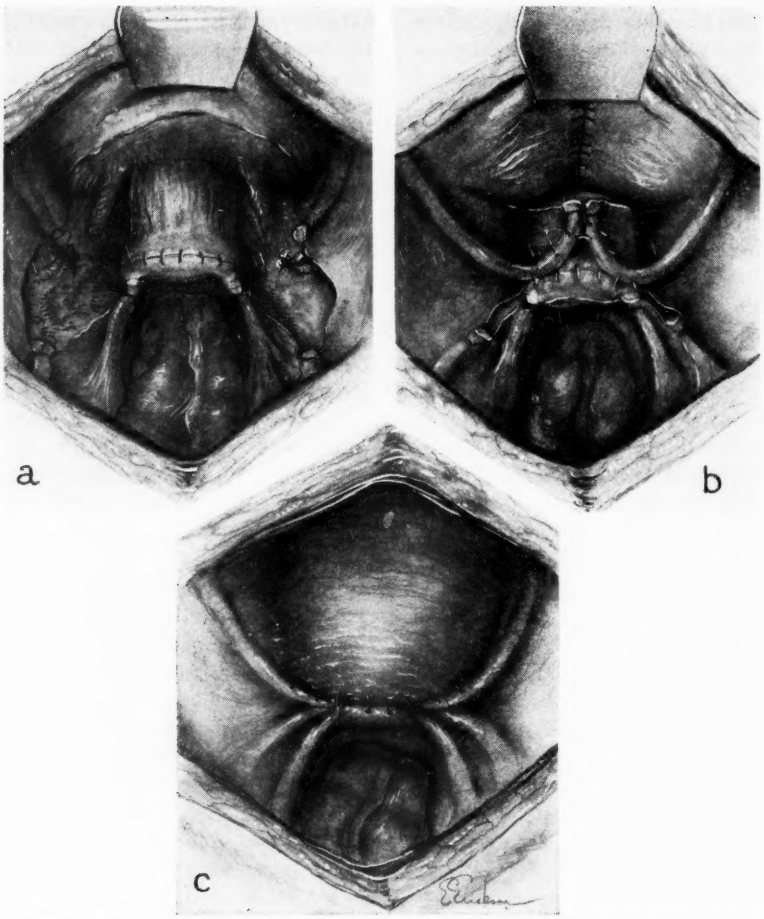

FIG. 2. a, The uterus has been removed and the vagina closed. b, The pubovesicocervical fascia has been approximated. The round ligaments have been attached to the anterior vaginal wall approaching the pubovesical fascia. c, Completed procedure with peritonealization of the pelvic floor.

The Abdominal Approach for Repair of a Cystocele.—R. E. Speirs.

THE SURGEON AT WORK

THE ABDOMINAL APPROACH FOR REPAIR OF A CYSTOCELE

R. E. SPEIRS, M.D., F.A.C.S., Dodge City, Kansas

CYSTOCELE OF VARIABLE SIZE is a common complication following childbirth. Relaxation of the fascia, vaginal mucosa, and perineum permits the bladder to sag between the more resistant anterior pubovesical fascia and the uterus. The condition is accentuated with repeated pregnancies and the loss of muscle tone associated with aging. The symptoms depend upon the size of the cystocele, the residual urine, and the presence or absence of infection.

It is generally accepted that the perineal support gives away preceding the development of a cystocele. For this reason a perineal repair or posterior colporrhaphy is performed at the same time that the cystocele is repaired.

Forty cases of cystocele repaired by the abdominal approach over a period of 4 years are to be discussed. All patients have had a cystocele associated with pelvic disease which required abdominal surgical intervention. This procedure is not recommended for the cystocele in which pelvic disease is not present. The conventional vaginal route should be used in such instances.

The idea for the abdominal repair of a cystocele developed after seeing the improvement in relaxation following total hysterectomy. Apparently the procedure to be presented is not new; however, to the best of my knowledge, it has not been used to correct a cystocele but only to prevent its occurrence following hysterectomy.

The objective in the repair of a cystocele is to raise the urinary bladder floor back to its normal level and to maintain this position. Basically, it consists of mobilization of the bladder by freeing the pubovesicocervical fascia from the vagina and closing the defect between the pubovesical fascia and the uterus. It should make no difference whether this is done through the abdomen or the vagina. Modification of the technique is required in the abdominal repair of a cystocele, as in the vaginal repair, depending upon the tissue present.

TECHNIQUE

A Pfannenstiel or transverse incision is preferred, placed 1 inch above the pubic hair line. An incision made at a lower level restricts the retractility of the rectus muscles, so that the exposure is decreased. After the peritoneal cavity has been opened a general exploration of the abdominal contents is carried out. If the pathologic condition present in the pelvic organs does not interfere with exposure, the bladder dissection is carried out first. Traction on the uterus gives better exposure and facilitates dissection by keeping the vagina under tension. If the pelvic disease interferes with exposure this condition is attended to first, and the bladder dissection is completed later.

The uterovesical peritoneal fold is cut transversely and reflected anteriorly to expose the bladder. In large cystoceles this fold and the bladder are well down on the vagina instead of overlying the cervix. The bladder dissection is started in the midline in the manner used for a hysterectomy. The dissection should be performed beneath the pubovesicocervical fascia and this structure should be kept on the bladder side. Generally, this fascia is located more easily from above than at vaginal repair of a cystocele.

The musculofibrous wall of the vagina has a whitish appearance and is easily distinguished

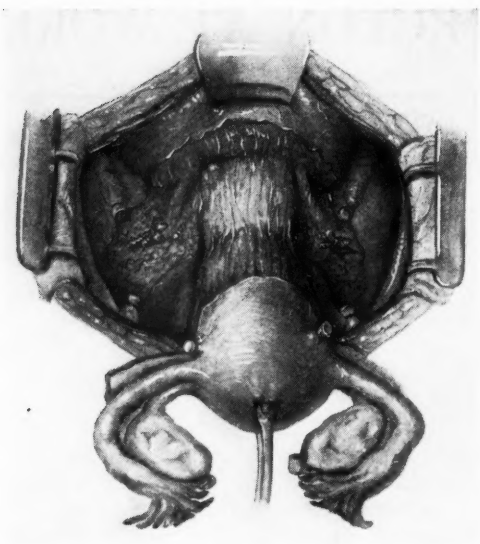

FIG. 1. The uterus and attached structures have been severed and pulled up. The bladder has been dissected free from the vagina and the ureters are exposed.

from the more vascular fibromuscular pubovesicocervical fascia. The dissection should be done gently as this tissue, which varies considerably in thickness, is prone to bleed, especially along the lateral edges of the vagina. When the vesicovaginal space is entered, the bladder is freed from the vagina down to the pubovesical fascia. The structures are more easily mobilized in the midline than laterally. Sharp and blunt dissection are necessary. It is always safer to carry the dissection toward the vagina, as a hole in it will be inconsequential, whereas one in the bladder, if unrecognized, may result in a vesicovaginal fistula.

Care must be taken not to mistake the ureters for bands and cut them as they swing around the vagina to enter the bladder. As the ureters pass behind the uterine arteries, they are about 2 centimeters lateral to the cervix. At this point the ureters are quite vascular, being enveloped by the vaginal and vesical plexus of veins. The ureters pass medially approaching the lateral edge of the vagina and then pass anterior to it, entering the base of the bladder. There is considerable variation in the course of the ureters across the pelvic floor to the bladder. The ureters lie from 1 to 3 centimeters lateral to the vagina at the level of the internal os. They can be very difficult to identify, especially in an obese patient. The usual appearance of the ureter is that of a piece of perivesical fat, as it passes through the perivesical tissue to enter the bladder. By very careful palpation, the ureter can frequently be felt to roll between the fingers. It is strongly suggested that ureteral catheters be inserted before the operation until one becomes familiar with the various positions of the ureters. Ureteral catheters should be placed in all obese patients.

After the bladder has been freed from the vagina down to the pubovesical fascia, the pubovesicocervical fascia is approximated in the midline with a running suture of No. 0 chromic catgut. Care must be taken not to penetrate the bladder with a resultant vesicovaginal fistula. The pubovesicocervical fascia varies considerably in patients. Some patients have well developed and definite layers of tissue which give good strong support. In other patients the fascia is so thinned out that it can hardly be recognized. In this latter group, one must not imbricate the base of the bladder in an effort to obtain stronger support for the bladder. A deformity of the trigone may result in dysuria.

At this point, total hysterectomy or other pelvic surgery indicated is completed. The supporting structures of the uterus are cut as close to it as possible. Variations for the support of the vagina and bladder are adopted depending upon the length of the remaining structures. The round ligaments are sutured to the lateral edge of the vagina, as far laterally on the round ligament as possible without causing undue tension. The medial portion of the round ligaments are then sutured as far down on the vagina beneath the bladder as length permits, interrupted No. 0 chromic catgut being used. Ideally, the ligaments should extend to the posterior edge of the pubovesical fascia. The vagina is supported by a suture through the uterosacral, round, and cardinal ligaments, anchored to the angle or midportion of the vagina, depending upon the length of these structures.

The bladder proper will then rest well up on the structures supporting the vagina. The pelvic floor is peritonealized, and the abdomen is closed anatomically. The patient is then put in stirrups and redraped. Occasionally, there is a redundance of vaginal mucosa around the urethra giving the appearance of a urethrocele. This is the result of inadequate freeing of the vaginal

mucosa. This excess mucosa can quickly and easily be dissected free and excised. The pubovesical fascia can be tightened, as indicated, with interruped No. 0 chromic catgut, and the vaginal mucosa closed. The rectocele is then repaired in the conventional manner.

Postoperative care of the bladder does not differ from the usual cystocele repair. A Foley catheter is placed in the bladder for continuous drainage for 4 days. After removal of the catheter the patient is catheterized after each voiding until the residual urine is 3 ounces or less on 2 successive catheterizations. Most patients are able to empty the bladder adequately upon removal of the catheter. In a few cases the catheter slipped out within 24 hours, and the patient was able to void. One patient required occasional catheterizations for 10 days depending upon the condition of her "nerves" when the desire to void arrived. The average time before adequate emptying of the bladder recurred was 6 days. Despite chemotherapy and antibiotic therapy a moderate percentage of these patients had a postoperative cystitis. The average period of hospitalization was 9 days.

There have been 2 recurrences of the cystocele; 1 was in the first patient operated upon. She is aware that her bladder protrudes somewhat but it is asymptomatic at present, and her urinalysis is normal. The second recurrence was in a patient who had an excellent immediate result, but over the past year she has had a symptomatic recurrence.

On postoperative examination the bladder is well elevated and the floor feels firm. The pelvic supporting structures can be palpated from 1 to 2 inches behind the pubovesical fascia. The vaginal mucosa is more loosely attached and more freely movable because of elimination of the vaginal incision. There have been no complaints of vaginal shortening or dyspareunia.

The technique has been changed as the number of cases and follow-up examinations have increased. In the first 5 cases, the bladder was freed from the vagina down to the pubovesical fascia. The vagina was opened and a wedge of mucosa removed as in vaginal repair. This was technically difficult, especially in a patient with a deep pelvis. In just such a case, with a large cystocele, severe bleeding was encountered. It seemed advisable to discontinue the abdominal repair of the cystocele. The vaginal wedge was not excised, but the bladder was mobilized and elevated, as if it had been done. Upon completion of the pelvic surgery, the patient was placed in the lithotomy position to repair the cystocele and rectocele. The bladder was found to be well elevated and supported so that further surgery was not indicated. The patient has an excellent result. Since this case the anterior vaginal wedge has not been removed.

SUMMARY

To reiterate, the major difficulties encountered in the abdominal repair of a cystocele were:

1. In the female with the deep pelvis upon whom it is difficult to do a total hysterectomy a cystocele might well be repaired in the conventional manner from below, as it is necessary to have good exposure below the cervix to complete this operation abdominally.

2. The greatest danger of this procedure is ureteral damage. The ureters may be damaged: (a) in the mobilization of the bladders, (b) during attempts to control hemorrhage which is prone to occur from the pubovesicocervical fascia, (c) in suturing the supporting structures of the vagina, and (d) in peritonealization of the pelvic floor. Since the bladder is freed from above downward the ureters are involved in the dissection. It is suggested that ureteral catheters be placed in the first few cases so that a ureter will not inadvertently be cut or tied.

3. There is a tendency for the dissection of the vagina not to be carried downward far enough. As a result, at the completion of the operation, there is redundant mucosa in the urethral area which gives the appearance of a urethrocele. This condition can be easily corrected at the time the rectocele is repaired.

The operative procedure described for the abdominal repair of cystocele has given very satisfactory results. It is generally an easier and a more rapid method than the conventional vaginal approach. The bladder is mobilized more extensively than is usual from below and this method should give a better functional result. The procedure described has been used to a lesser extent by pelvic surgeons in elevating the bladder at the time of a hysterectomy, but to my knowledge there has been no report of its extended use in the repair of a large cystocele.

A SIMPLE RETAINER FOR SMALL BOWEL DURING INTRA-ABDOMINAL OPERATIONS

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AN EXTENSIVE intra-abdominal operation is greatly simplified if the small bowel can be excluded from the field of operation without the use of multiple gauze packs and retraction. Procedures have been described to accomplish this condition, but they usually require some special bag, material, or apparatus.

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The simple maneuver illustrated in Figure 1 is readily available to any operator in practically any surroundings.

The excluded bowel remains visible, warm, and moist and permits exposure in the abdomen almost as readily as it does in the thorax. The abdominal cavity is relatively empty subsequent to isolation of the bowel in a thin-walled retainer.

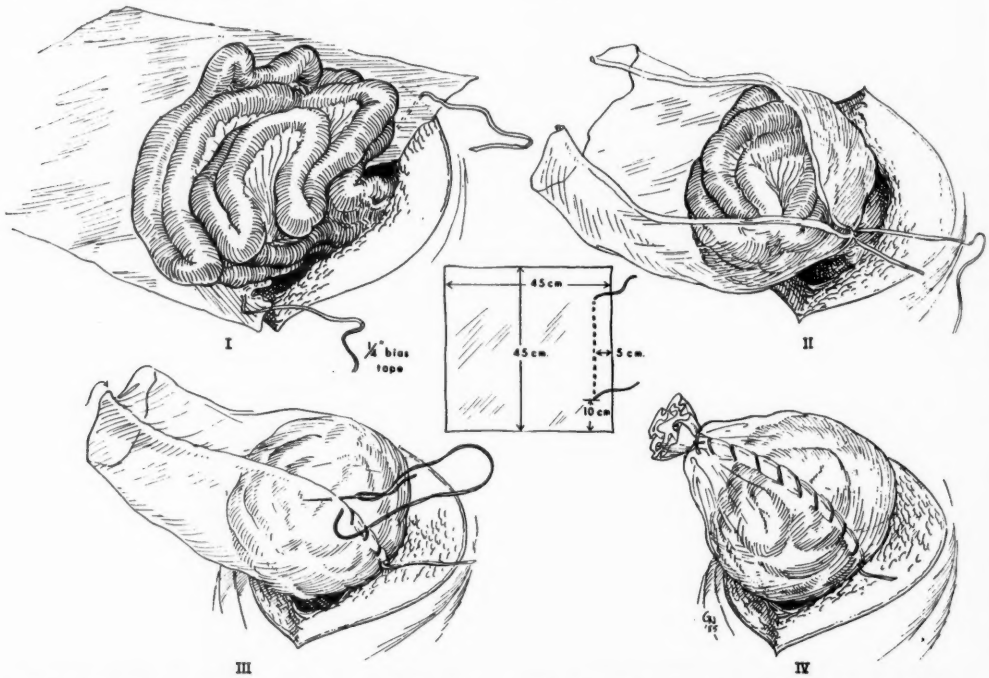

FIG. 1. Illustration showing method of excluding the small bowel from the operative field. The small central inset shows a square of sheeting 45 by 45 centimeters. This material may be cloth, rubber, or plastic. A thin, transparent, boilable plastic sheeting is preferred. A quarter inch bias tape (75 cm. long) is threaded onto a Keith needle and inserted as a purse-string 5 centimeters from one edge as shown. It is important to place this purse-string 5 centimeters back from the edge so as to prevent the bowel slipping out of the retainer. This sheet of material is slipped under the small bowel (I), and the purse-string is pulled up quite snugly and tied well down on the root of the mesentery (II). The purse-string may be tied snugly without compromising the circulation and must be snug to prevent the bowel from creeping out. The tape is tied with one end long. This long end is used to sew the rolled edges of the sheet and is tied again to close the end forming a bag (III). The excess material is cut away. The retainer should be longer than is needed to contain the bowel, because a relatively long sack will facilitate manipulation of the small bowel (IV). Cut the purse-string to release and remove the retainer.

THE SURGEON'S LIBRARY

The Book Shelf

THE HISTORY OF PLASTER OF PARIS BANDAGES

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THOSE WHO TREAT FRACTURES and use plaster of Paris bandages every day must sometimes wonder about the origin and use of the material and why it has such a specific name. Just as with Paris green and Bismarck brown, there must be a story behind the term and so there is, although the use of plaster of Paris bandages is relatively recent from a historical viewpoint.

Gypsum—or in its crystalline form, selenite, or in its smooth marblelike form, alabaster—is hydrous calcium sulfate Ca $SO_4.2H_20$. In its natural state, it is mixed with impurities such as iron, silicates, and carbonates. When heated to 120 degrees C. it gives off the water of crystallization and becomes anhydrous plaster of Paris; when immersed in water it again unites with the water, forming firm interlocking crystals of the monoclinic system which harden quickly. The gypsum quarries of Montmartre, in the north of Paris, lying in the tertiary strata and rich in fossils, have been worked for centuries.

The substance which we now use was well known to the ancients for the pyramids of Egypt contain excellent examples of gypsum plaster work executed not less than 4,000 years ago. Herodotus (484–425 B.C.) mentions its use and properties, and Dioscorides (c. 50 A.D.) speaks of σεληνίτης so-named from the moon, probably in allusion to the soft moon-like reflection coming from some of its faces. Galen (131–201 A.D.) recommended it as a hemostyptic, but its great value in the treatment of fractures was overlooked by physicians for millenniums.

In the Hippocratic writings a dressing containing glue of wheat meal was prescribed for the treatment of nasal fractures; the addition of incense or rubber was supposed to increase its adhesive qualities. After manipulation, clubfeet were bandaged firmly and fixed with a mixture of wax and resins. The same measures were employed for fractures of the long bones by Celsus at the start of the Christian Era, by Galen, and by Paul of Aegina (625–690 A.D.) in the Byzantine period; and Pliny, in the court of Augustus, had recounted the death of a patient who had taken gypsum internally for severe gastric pain.

The first report of the use of plaster for fractures comes from the Arabian physician, Rhazes, who was born in 860 A.D. and lived to an advanced age in Ray, a large city in Persia. He wrote: "But if thou make thine apparatus with lime and white of egg it will be much handsomer and will not need to be removed until the healing is complete." Lime was obtained by his directions from the incineration of certain sea shells (conchae). The Persian, Abu Mansur, records this method again in the tenth century.

Medieval and Renaissance surgeons in the West apparently remained in ignorance of these advances. Their favorite Arabic author, Avicenna, never transmitted this knowledge to them. With minor variations the description of Ruggiero Frugardi in 1170 A.D., of the method

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in practice at Salerno was as follows: after reduction the broken limbs were covered with oakum, moistened with egg albumen, or wrapped with a rag to which a rather tough dough of flour and egg albumen was applied. This dressing was completed by splints and further bandages. One does not wish to imagine the odor. Teodorico Borgognoni (1205–1297), Bishop of Cervia, whose distinction it was to recommend, but not have accepted, the aseptic treatment of wounds, followed the same recipe, adding honey, pork fat, and more egg white, this time beaten. Under the influence of Ambroise Paré (1510–1590), the hardening dressing was nearly forgotten. Surgical interest reverted mainly to the technical improvement of splints.

One can but surmise what misery, pain, and long-suffering were caused by these methods. How many cases of sepsis, how many amputations and deformities must have resulted, and what frightful stenches emitted from these oozing culture media. However, peasant, noble, and physician alike were accustomed to such affairs in medieval times and they are seldom remarked upon, simply accepted.

Californians will be interested to learn that insofar as the fixation of fractures goes, the Indians native to the coast of California were at least abreast of the surgeons in the leading centers of western Europe. Rollin, surgeon on the La Perouse voyage of 1786 which put in at Monterey, records (3), "they place the ends of the broken bones in contact; keep them in that position by a bandage; and placing the limb in a case of bark, tied fast around it by leather thongs, the patient is made to remain perfectly quiet until the parts are perfectly united."

Most of the ideas for the improved hardening of dressings since the end of the eighteenth century have emanated from military surgeons. Jean Dominique Larrey (1766–1842), Napoleon's chief surgeon, continued to splint, wrap with a cloth, and to apply a concoction of camphor, alcohol, lead acetate, and egg white. The method is said to have been too costly for widespread use on the battlefield.

In 1835, Louis Seutin, the Inspector General of the Belgian Army, produced a starched dressing which was widely adopted. It consisted of bandages moistened with solutions of starch which were applied around splints of cardboard. These splints were previously softened in water and then also treated with starch. Drying required 48 hours during which time the bone fragments might slip and lose their position.

The English Consul at Basra on the Persian Gulf, W. Eaton, learned in 1794 of the Arabian method of casting in plaster which had been followed for centuries. I quote from his letter to Dr. George Guthrie, of Petersburgh: "An Arab, one of my soldiers, having had his leg and foot fractured, and almost crushed to pieces by the falling of a field piece upon him, which forced the ends of the bone through the skin, our European surgeons proposed immediate amputation above the knee. . . . The inhabitants of those parts will never consent to have a limb cut off; so that the people undertook his cure in their own way . . . placed him on an oiled mat, they reduced the bones and shattered parts in as good form as they could, . . . they first poured the Paris plaster under his leg, till it rose to such a height as to touch its whole lower surface and part of the thigh; placing at the same time a few pieces of hollow reed at proper distances, . . . When this plaster cushion had become firm, the whole leg was next covered with the same Paris plaster, so as to enclose it completely, and on hardening, to form a light case or plaster boot . . . the accident happened in May and on the Colonel's return from a second expedition in September, he found the patient walking about, and enjoying the use of his leg, in spite of considerable deformity." Peter Hendrichs in 1814 used the same method in Gröningen with good results. It is thought that he learned of it through Froriep who knew of the Moors using it in North Africa. Intimations of and accounts of practice in India and in the Arab world reached Europe from time to time, but were little-heeded."

Sédillot describes an apparatus in use among the Arabs, made of leather, pierced with rows of holes through which were drawn sticks of polished wood to give stiffness, and he states that these sticks were withdrawn to allow pus to exude, showing that they recognized the great advantages of an apparatus for compound fractures which did not require removal in order to dress the wound, and he also says that, "the Arab surgeons make the pressure more agreeable and more uniform by wrapping the limbs in moss, and they make their apparatus immovable by covering it with a layer of clay, which in drying acquires the solidity of plaster."

These communications seem to have lain long unnoticed and it was not until 1828 that Keyl

and Klugge at the Berlin Charite commenced the systematic use of plaster casting (but not bandaging). Ten years later in the same hospital Dieffenbach used the same technique for club-feet after subcutaneous tenotomy. Their method was to place the greased limb in a wooden box, the inner surfaces of which were also greased, and to pour in liquid plaster of Paris until the limb was nearly, but not completely covered. When the plaster had set the wooden box was removed, its sides having been held together by hooks.

Modifications were practiced in Germany by Richter and Hubenthal and the news must have reached England for Sir Astley Cooper cites a case so treated by G. Bond of Glastonbury. In 1838, Lafargue de St. Emilion modified Seutin's starch apparatus by mixing with the starch, equal amounts of powdered plaster of Paris which, he said, had the quality of becoming "instantanement solidifiable." His contemporaries seem to have been little impressed.

Toward the end of the year 1851, a Belgian army surgeon, Antonius Mathijsen, commenced rubbing plaster of Paris into coarse woven cotton patterns cut to the shape of the injured limb, but in his first publication in 1852 he mentions the use of roller bandages so impregnated and in his later works refers almost entirely to gypsum bandages 5 to 10 centimeters in width. Mathijsen is the author of instructions still in use today to preserve the bandages in metal drums, to immerse them in water for a minute or until no more bubbles arise, and to work a dry padding around the limb before application of the plaster cast. Among the many advantages he listed were its cheapness and its value on the battlefield where a shortage of water might be adjusted by the use of urine.

Seutin (of the starch cast) attacked Mathijsen long and bitterly, throwing the weight of his authority and position in an overbearing manner. Other opponents claimed that the cast broke easily, would not harden, injured the skin, and was too expensive. Mathijsen also had to defend himself against unjustified claims of priority in certain modifications. His friend and fellow medical officer, J. H. P. vandeLoo, who became an ardent advocate of the method, supplemented well the inventor's modesty. Within a few years he had lectured and given demonstrations in Paris, Brussels, Lyons, Cologne, and many clinics in France and western Germany.

FIG. 1. Antonius Mathijsen. (Taken from *Opuscula Selecta Neerlandicorum*. Amsterdam, 1878.)

By 1856 the value of the plaster of Paris bandage had become appreciated and was being recommended in the publications of the Society of Surgery and Obstetrics of Amsterdam and of the Society of Physicians in Vienna. The method was used extensively by the Germans in the Franco-Prussian War.

The introduction of plaster of Paris bandages to America was furthered by the teachings and writings of St. John of New York, who emphasized that the splint must be fitted to the limb, not the limb to a particular splint. He devised methods of padding with cotton wadding and often split the wet plaster down one side of the limb with a shoemaker's knife. By 1872 he was able to present a large series of plaster treated cases from Bellevue Hospital.

Mathijsen was honored in many ways: Knighthood of the Order of the Netherlands, Lion and Oak Crown of Luxemburg, honorary membership in the medical societies of a dozen foreign cities. Mathijsen eventually visited America for the Centennial Exposition of 1876 and demon-

strated his method in Philadelphia. He died in 1878 and was buried in Hamont, Belgium. On October 24, 1946 a delegation of the International Society of Orthopedic Surgery including Henry Meyerding of Rochester, Minnesota, dedicated a monument to his memory in Budel, Holland, Mathijsen's birthplace.

The Soviet surgeon Yudin writing with strong chauvinism in 1944 stated: "Pirogoff, quite independently of Mathijsen, began the treatment of fractures by using a plaster cast a year and a half before the Crimean War, i.e., at the very beginning of the year 1853. He was the first surgeon in the world who used this method in military surgery and on a very large scale during the siege of Sevastopol. Pirogoff's *The Principles of General War Surgery* . . . is a classical work on field surgery without an equal in any country in the 19th century."

The western world continues to accord Mathijsen priority.

REFERENCES

1. Abu Mansur, Muwaffak. Die Pharmakalogischen Gruendsatze nach dem Urtext uebersetzt von Abdul-Chalig Achundow. S.230, Nr. 382. In: Historische Studien aus dem Pharmakalogischen Institute der Universitaet Dorpat, edited by R. Kobert. 3rd ed. Halle, 1893.
2. Cooper, Astley. A Treatise on Dislocations and Fractures of the Joints. P. 166. Philadelphia: Lea and Blanchard, 1844.
3. Eaton, W. Account of the Arabian mode of curing fractured limbs. Medical Commentaries for the year 1794, Philadelphia, 1795, 41: 167.
4. Mathijsen, Antonius. Nieuwere wijze van aawending van het gipsverband bij beenbreuken; eere bidrage tot de militaire chirurgie. Harlem, 1852.
5. Milet-Mureau. Voyage de la Perouse. P. 264. Paris, 1789.
6. Pirogoff, Nicolaus. Der Gypsklebeverband. Leipzig: Druck and Verlag von Breitkopf and Hartel, 1854.
7. Rhazes. Quoted by Bacon, L. W. Plaster of Paris bandages. Bull. Soc. M. Hist. Chicago, 1923, 3: 122.
8. St. John, Samuel B. Plastic apparatus in surgery. Am. J. M. Sc., 1872, 64: 75.
9. Sedillot. Gaz. méd., Par., 1838, 135.
10. Yudin, Serge S. The treatment of war fractures of the femur. Surg. Gyn. Obst., 1944, 78: 1.

Reviews of New Books

THE 1954 EDITION of *Collected Papers of The Mayo Clinic and The Mayo Foundation*[1] contains an unusual number of papers regarding current controversial problems in the various specialities as well as those in the general practice of medicine. Obviously, one cannot select any group of subjects as being the most important, but the material is so arranged that each reader may easily seek and find papers most interesting to him.

The general practitioner should enjoy reading the entire volume. Practically all of the articles dealing with the alimentary tract are pertinent to problems seen in general practice. Everyone will find many, if not all, of the articles listed under ductless glands, physical medicine, and miscellaneous papers informative and extremely helpful in the everyday practice of medicine.

The diagnostician cannot read the section on blood and circulatory organs and not arrive at a true evaluation of the material presented. An excellent example of such a paper is "Unusual Forms of Heart Disease." Even if the reader does not agree with it in whole or part, he cannot question the effect of intellectual stimulation. The thoracic and neurosurgical sections should entertain those concerned with diagnostic problems.

The general surgeon likewise should enjoy most of the contents of this book. Under the section of alimentary tract there are varied and unusual presentations. Papers, such as, "Liver Biopsy," "Chronic Ulcerative Colitis," and "Lesions of the Pancreas of Surgical Interest" are but a few examples.

In all, this volume contains an excellent group of papers representative of the diagnostic and therapeutic acumen of the staff physicians and surgeons at the Mayo Clinic. This book would be a helpful addition to any doctor's library. —*Vinton E. Siler.*

THE 1954 EDITION of the *Surgical Forum*[2] of the American College of Surgeons encloses in a single volume all the scientific papers delivered at the Surgical Forum sessions at the November 1954 meeting in Atlantic City. That surgery of the present and of the future is based on a firm groundwork of physiology, biochemistry, and biophysics is better demonstrated nowhere than in this collection.

The present day interest in problems associated with surgery of the heart and blood vessels is patently evident by the fact that approximately one-third of the volume consists of papers devoted to investigative studies in this field. Further experiences are reported by those operating upon the cardiac chambers and valves with both open and closed methods. Refinements in technique and supportive measures, such as the use of hypothermia, are discussed and evaluated.

Methods described for testing the patency of portacaval shunts include the use of radioactive sodium injected into the rectum, after which the appearance of this substance is recorded in time at the level of the brachial artery. Other authors discuss a chemical method based on the difference between the oral ammonium citrate tolerance curve when portal blood bypasses the liver in contrast to the curve with normal liver perfusion.

Various methods are described for the preparation and sterilization of vascular homografts. The fate of such grafts in the experimental animal as well as in the human is further clarified by a number of papers in the section on "Blood Vessels and Circulation." It seems evident that, at the present time, pliable plastic prostheses are suitable for aortic replacement in man.

The problem of esophagitis incident either to hiatus hernia or to proximal gastric resection remains at least partially unsolved. Various valve-like mechanisms have been devised in order to prevent reflux esophagitis. It is encouraging to note the success of such procedures in the experimental animal. The use of an interposed segment of jejunum to replace the cardioesophageal junction has apparently produced satisfactory results, in that the jejunal transplant appears to act as a physiologic sphincter as shown by the absence of jejunitis in this segment on microscopic study. The etiology of esophagitis is discussed in several papers and the mechanical factor, i.e., the reflux of gastric contents beyond an incompetent cardiac sphincter, is emphasized.

Of particular significance in the section on "Liver and Pancreas" is the work of Thal and associates, who suggest that the underlying lesion of acute pancreatitis is a fibrin-platelet capillary and vascular thrombosis associated with local ischemia, leading in turn to necrosis. Methods of differentiating obstructive from nonobstructive jaundice by injection of fluorescein into the extrahepatic biliary ducts and by determination of the serum mucoprotein levels are discussed and evaluated. The uniformly low levels of mucoprotein in hepatocellular disease as compared to the constant elevation seen in extrahepatic obstructions suggest that this test may well be of considerable promise in the differential diagnosis of jaundice.

The maintenance of adequate caloric intake in patients with severe abdominal surgical problems is an investigative field of considerable moment. Several

[1] COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Edited by Richard M. Hewitt, B.A., M.A., M.D., A. B. Nevling, M.D., John R. Miner, B.A., Sc.D., James R. Eckman, A.B., M.A., Ph.D., M. Katharine Smith, B.A., Carl M. Gambill, A.B., M.D., M.P.H., Florence Schmidt, B.S.E., and George G. Stilwell, A.B., M.D. Vol. XLVI. 843 pages, 189 figures. $12.50. Philadelphia, London: W. B. Saunders Co., 1955.

[2] SURGICAL FORUM; PROCEEDINGS OF THE FORUM SESSIONS FORTIETH CLINICAL CONGRESS OF THE AMERICAN COLLEGE OF SURGEONS, ATLANTIC CITY, N. J., NOVEMBER 1954. Committee on Forum on Fundamental Surgical Problems: Harris B. Shumacker, Jr., M.D., F.A.C.S., Indianapolis, Chairman, J. Garrott Allen, M.D., F.A.C.S., Chicago, Bradford Cannon, M.D., F.A.C.S., Boston, Warren H. Cole, M.D., F.A.C.S., Chicago, Robert E. Gross, M.D., F.A.C.S., Boston, J. Albert Key, M.D., F.A.C.S., St. Louis, C. Hunter Shelden, M.D., F.A.C.S., Pasadena, Howard C. Taylor, Jr., M.D., F.A.C.S., New York, Samuel A. Vest, M.D., F.A.C.S., Charlottesville. 851 pages. $10.00. Philadelphia, London: W. B. Saunders Co., 1955.

interesting papers analyze and criticize various types of parenteral solutions. The high caloric value of fat preparations makes their use attractive in the maintenance of nutrition. However, except in minimal, ineffective concentrations, these substances produce hemolysis and other undesirable side effects. Experimental studies on this problem are properly being continued. Papers concerning the renal clearance of plasma expanders as well as the many other problems of body fluids and electrolyte metabolism are included in this section.

The relationship of the various steroids to the functional characteristics of certain types of cancer is considered in detail in several thought-provoking papers in the section on "Steroids and Cancer." The adrenal cortical function in shock and other pathophysiologic states is discussed from several aspects, i.e., the response to trauma, the adrenocortical reserve in debilitated surgical patients, and the response to surgery in elderly individuals.

The papers in the section on "Anesthesiology" emphasize the necessity of close liaison between surgeon and anesthesiologist. The everyday problems of the operating suite are discussed in terms of investigative studies designed to eliminate or at least clarify the major difficulties which sometimes occur in the anesthetized patient. The consequences of excess accumulation of CO_2 as well as studies in hypothermia are reported in this section.

The two concluding sections deal with "Burns" and "Shock and Wounds." The information in these sections is of great value because the approach is at the basic level of cellular function, the metabolism at the level of the local wound, and the manner in which systemic reactions are caused by the changes occurring in the local area.

This 1954 edition of the *Surgical Forum* of the American College of Surgeons represents a valuable collection of outstanding articles on the substance and practice of surgery. It must be acknowledged that in no other volume is the present and immediate future of surgery so aptly, comprehensively, and vividly presented. —*Orville F. Grimes.*

THE SEVENTH EDITION of the standard book *Pathology for the Surgeon*[3] under a new title-head has been rewritten and brought up to date with new chapters on wound infections, soft tissues, skin, endocrine glands, and the cardiovascular system. The first chapter of the book is to be commended. It re-emphasizes the need for a solid foundation in pathology for any clinical branch of medicine, mentions a much repeated, but all too often forgotten concept of limitations of histologic diagnosis. Each chapter is initiated by a table of contents which also provides a classification of the material discussed.

A section on general considerations which deals with pertinent anatomic and physiologic data is included. References at the end of the book are arranged for the reader's convenience; many older references have been deleted and replaced by more recent contributions. The chapter on the general pathology of tumors has been rewritten and except for minor typographic errors is commendable, more so because an attempt is made to explain the clinical vagaries of specific tumors in the light of their pathologic manifestations. The book is replete with photomicrographs, and the printing and binding of the book are excellent. The change in the color scheme of the cover reflects the change in the contents of the book the author has wrought in this edition. As in his other two accepted texts, Boyd continues to write in his inimitable style. His work fulfills the purpose for which the book was written and is recommended for surgeons, general practitioners, and pathologists. —*M. C. Wheelock.*

"SURGICALLY CONSIDERED, a dire need of exact and extensive anatomic knowledge exists today, as regards the varied patterns of the arterial blood supply to the supramesocolonic organs, for the textbook description and the general anatomic concept of the vascularization of these organs are markedly inadequate and misleading." Thus writes Nicholas A. Michels in his text *Blood Supply and Anatomy of the Upper Abdominal Organs with a Descriptive Atlas.*[4]

After 20 years of anatomic research, the author has dissected, collected, and presented his findings in a most lucid, concise, and accurate manner. The text consists of 316 pages and is divided into 14 chapters. Included is an excellent chapter on embryology, topographic relations and developmental anomalies, and collateral arterial pathways to the liver after ligation of the hepatic artery and removal of the celiac axis. One finds an excellent review of the literature, and an appropriate bibliography is given for each of the regions studied. Combined with the text is a descriptive atlas consisting of 172 illustrations, 166 of which are in color. The pertinent information written in the text is clearly illustrated in the atlas. Of particular interest, is the plate on the supramesocolonic vascular supply of a case of complete *situs inversus*.

It may be revealing to those interested in abdominal surgery and it certainly will be a surprise to most medical students to learn the conventional textbook description of the arterial blood supply of the liver occurs in only 50 per cent of the population. Also noted is the finding that in the general population some sort of an aberrant hepatic artery occurs in approximately every second body. The study of 150 plastic casts of the liver by the author's colleagues revealed that every major artery of the liver (normal, replaced, or accessory) supplies a definite segment of the hepatic parenchyma. Inadvertent ligation of one of these vessels causes necrosis of the liver parenchyma supplied by the ligated vessel. As suggested by the author and other men this may be a plausible reason for some causes of unexpected deaths following cholecystectomy and gastric resections. These are but a few of the important surgical correlations resulting from the author's anatomic dissections.

[3]PATHOLOGY FOR THE SURGEON. By William Boyd, M.D. (Edin.), Dipl. Psychiat. Edin., F.R.C.S. (Can.), F.R.C.S. (Lond.), M.R.C.P. (Edin.), F.R.S. (Can.), LL.D. (Sask.), D.Sc. (Man.), M.D. (Oslo). 7th ed. 737 pages, 547 illustrations (10 in color). $12.50. Philadelphia, London: W. B. Saunders Co., 1955.

[4]BLOOD SUPPLY AND ANATOMY OF THE UPPER ABDOMINAL ORGANS WITH A DESCRIPTIVE ATLAS. By Nicholas A. Michels, M.A., D.Sc. (Louvain). 581 pages, 172 illustrations (166 in color). $24.00. Philadelphia, Montreal: J. B. Lippincott Co., 1955.

Michels should be commended indeed, for his perseverance in completing such a detailed anatomic study. This is not just another textbook of compiled anatomic statistics, but a source of valuable information for the abdominal surgeon as well as the first year medical student. —*L. Lake Swigart.*

AN EXCELLENT ANATOMIC ATLAS of the skull and facial bones written by Lewis E. Etter is entitled *Atlas of Roentgen Anatomy of the Skull.*[5] It is particularly valuable to the practicing physician because the projections are those universally used in routine radiography of the skull, sinuses, and mastoids. The presentation is quite complete with photographs and radiographs in comparable projections. Probably the most outstanding feature of this atlas is the presentation of Etter's work on the disarticulated skull. Radiologists have had the privilege of seeing this at exhibits as well as in the radiologic journals. Comparable radiographs of the skull with and without the various bony components are demonstrated in routine projections. This approach enables one to positively identify all the various lines and markings which have in the past been rather confusing. Special sections by J. Brown Farrior on the temporal bone and by Samuel Henderson and Louise S. Sherman on the skull of the newborn infant enhance the value of the atlas.

This atlas is highly recommended to the radiologist, the neurosurgeon, and all physicians who study routine radiographs of the skull and facial bones. The roentgenograms are excellently reproduced in the radiographic image. —*R. Burns Lewis.*

IT HAS BEEN SAID that anything good is worth waiting for. Certainly this maxim is true when one considers Volume II of the fourth edition of *Fractures and Joint Injuries*[6] by Sir Reginald Watson-Jones. Those who are interested in fractures have been waiting for this volume for several years. In his inimitable manner the author has again revised this excellent text. It appears that this book might logically be recommended as the best text in the English literature and probably in the world literature on the treatment of fractures and joint injuries.

Several notable changes are found in the second volume of the fourth edition. Previously, the reader had gained the impression that the author advocated that the surgical approach to the treatment of fractures be used only as a last resort and that he advocated it rather reluctantly even then. He still emphasizes the importance of nonoperative therapy when possible, but in certain fractures, notably those of the shaft of the femur, selected fractures of the ankles, and others, he now advocates the operative approach in the primary treatment. The additions to the chapter on injuries of the shoulder are very well done, and if one follows the principles and ideas set forth by the author, much less trouble from this joint will be met in rehabilitating the patient who has received such an injury.

The new discussion pertaining to the mechanism of fractures of the upper part of the femur in the region of the hip brings this chapter up to date. It is gratifying to note that the author is very willing to change his mind when irrevocable evidence is presented as to the mechanism of a fracture or as to a better way of treatment. He advocates intramedullary fixation of certain fractures of the shaft of the femur which the reviewer believes are a little high in the shaft for such therapy. Likewise, some of the fractures of the shaft of the femur may be a little low for fixation with a single intramedullary rod.

Fixation of the medial malleolus with one screw is the best form of therapy for many fractures of the ankle, and the author does not hesitate to make such a statement. It is interesting to note that minor sprains of the ankle are no longer treated by prolonged adhesive taping as had been advocated previously by the author. He still stresses, however, that one must make absolutely certain that any injury about the ankle represents a sprain and not a subluxation of the talus or a diastasis of the distal tibiofibular joint.

The chapter devoted to the rehabilitation of the paraplegic is very encouraging and will be a boon to those who have the opportunity of caring for these unfortunate persons.

In writing this edition the author again called not only upon his vast experience but also upon that of many gifted associates and others to present the very latest and most up-to-date ideas based on sound principle. He has written and profusely illustrated this volume in just as interesting and dogmatic a manner as he did the previous editions. Were it not that he is willing to change his ideas, the dogmatic approach might be very disturbing; however, in teaching, this approach usually is the best, and after all, this is a teaching text. This volume is recommended to all who are called upon and have the privilege to treat and rehabilitate patients who have received fractures and joint injuries of any kind.

Volume II as well as Volume I of this edition represents a monumental task and a tribute to an outstanding leader in orthopedic surgery.

—*Paul R. Lipscomb.*

THE SECOND EDITION of Claude E. Welch's *Surgery of the Stomach and Duodenum*[7] will be received just as enthusiastically as his first edition. He offers in this edition additional information as well as subject matter. The original format has not been changed and emphasis on techniques rather than on detailed discussion has been maintained. The book is planned as a practical guide particularly for younger surgeons; however, older and experienced surgeons will find in it a thoughtful refresher course in surgical procedure.

[5] ATLAS OF ROENTGEN ANATOMY OF THE SKULL. By Lewis E. Etter, B.S., M.D., F.A.C.R. With a section on The Radiographic Anatomy of the Temporal Bone by J. Brown Farrior, M.D., F.A.C.S. And a section on The Roentgen Anatomy of the Skull in the Newborn Infant by Samuel G. Henderson, M.D., F.A.C.R., and Louise S. Sherman, B.S., M.D. 215 pages, 239 plates. $14.75. Springfield, Ill.: Charles C Thomas, 1955.

[6] FRACTURES AND JOINT INJURIES. By Sir Reginald Watson-Jones, F.R.C.S., F.R.A.C.S. (Hon.), F.A.C.S. (Hon.), F.R.C.S.E. (Hon.), M.Ch.Orth., B.Sc., M.B. 1073 pages, 1613 illustrations. $22.00 (2 vols.). Baltimore: The Williams & Wilkins Co., 1955.

[7] A HANDBOOK OF OPERATIVE SURGERY; SURGERY OF THE STOMACH AND DUODENUM. By Claude E. Welch, M.D., D.Sc. (Hon.). 2nd rev. ed. Illustrated by Muriel McLatchie Miller. 370 pages, 79 plates. $9.00. Chicago: Year Book Publishers, Inc., 1955.

The handbook covers the most common and important operations that are performed on the stomach and duodenum. There is a brief discussion of the various surgical procedures employed with excellent line drawings giving an accurate portrayal of the steps in the various operations. The recommended operations are those currently in use at the Massachusetts General Hospital. Usually alternative techniques that have enjoyed popularity are included. Emphasis has been placed on the indications for the various procedures and on the selection of safe rather than the brilliant operations. Dr. Welch has added in this edition an interesting historical review of the development of surgery of the stomach and duodenum which should be of added interest to the young surgeon.

—*Harold L. Method.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

COMPLICATIONS OF REGIONAL ANESTHESIA; ETIOLOGY-SIGNS AND SYMPTOMS-TREATMENT. By Daniel C. Moore, M.D. 291 pages, 51 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1955.

THROMBOEMBOLIC DISEASE. By Geza De Takats, M.D., M.S., F.A.C.S. 55 pages. $2.25. Springfield, Ill.: Charles C Thomas, 1955.

OBSTETRICAL PRACTICE. By Alfred C. Beck, M.D., and Alexander H. Rosenthal, M.D. 6th ed. 1066 pages, 969 illustrations. $12.00. Baltimore: The Williams & Wilkins Co., 1955.

ATLAS OF GENERAL SURGERY. By Joseph R. Wilder, M.D. 222 pages, with 101 plates. St. Louis: The C. V. Mosby Co., 1955.

GERMAN-ENGLISH MEDICAL DICTIONARY. By W. O. Goulden, B.S. (Hons), Dr. phil. 513 pages. Boston: Little, Brown & Co., 1955.

MODERN TRENDS IN OBSTETRICS AND GYNAECOLOGY (Second Series). Edited by Kenneth Bowes, M.D., M.S. (Lond.), M.B., Ch.B. (L'pool), F.R.C.S., F.R.C.O.G. 407 pages, 176 illustrations. $12.00. New York and London: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1955.

SURGERY IN WORLD WAR II. HAND SURGERY. Edited by Sterling Bunnell, M.D. Medical Department, United States Army. 447 pages, 224 illustrations. Washington, D. C.: Office of the Surgeon General, Department of the Army, 1955.

MEDICAL SUPPORT OF THE ARMY AIR FORCES IN WORLD WAR II. By Mae Mills Link and Hubert A. Coleman. Department of the Air Force. 1027 pages, illustrated. Washington, D. C.: Office of the Surgeon General, USAF, 1955.

THE SURGICAL TECHNIC OF ABDOMINAL OPERATIONS. By Julius L. Spivack, M.D., LL.D., F.A.C.S. 5th ed. 931 pages, 1037 illustrations on 495 figures. $17.50. Springfield, Ill.: Charles C Thomas, 1955.

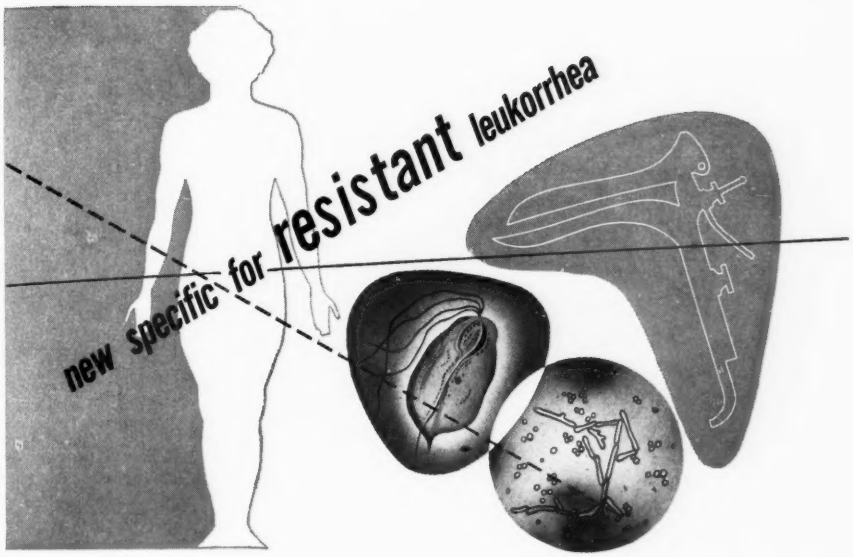
MAYES' HANDBOOK FOR MIDWIVES AND MATERNITY NURSES. Revised by F. D. Thomas, S.R.N., S.C.M., Midwife-Teacher's Diploma. 5th ed. 460 pages, 167 illustrations. $4.75. Baltimore: The Williams & Wilkins Co., 1955; London: Baillière, Tindall, & Cox, 1955.

CLINICAL NEUROSURGERY. Proceedings of the Congress of Neurological Surgeons, New York, New York, 1954. Vol. II. 173 pages, 54 illustrations. $6.75. Baltimore: The Williams & Wilkins Co., 1955.

CLINICAL STAGE CLASSIFICATION OF MALIGNANT TUMORS OF THE BREAST (1956 DRAFT). Research Commission, International Union Against Cancer. Committee on Clinical Stage Classification and Applied Statistics. 33 pages, illustrated. Paris: International Union Against Cancer, 1955.

THORACIC SURGICAL MANAGEMENT. By J. R. Belcher, M.S., F.R.C.S., and I. W. B. Grant, M.B. (Edin.), F.R.C.P. (Edin.). Foreword by Sir Clement Price Thomas, K.C.V.O., F.R.C.S. 2nd ed. 216 pages, 78 illustrations. $4.75. Baltimore: Williams & Wilkins Co.; London: Baillière, Tindall, & Cox, 1955.

ATLAS OF BRONCHIAL LESIONS IN PULMONARY TUBERCULOSIS; A CLINICAL AND MORBID-ANATOMICAL STUDY. By C. Dijkstra, M.D. 128 pages, 131 illustrations. $11.00. Springfield, Ill.: Charles C Thomas, 1955.



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